CV/L-H0055 27-34-P25784

BRITISH JOURNAL
OF
ANAESTHESIA

Editor of General Issues
G. SMITH
B.Sc., M.D., F.R.C.Anaes.

Editor of Educational Reviews
L. STRUNIN
M.D., F.R.C.Anaes., F.R.C.P.C.

Volume 70
1993

34

Published by
Professional and Scientific Publications
BMA House
Tavistock Square
London WC1H 9JR

Typeset in Great Britain by
the University Press, Cambridge

34

CONTENTS

JANUARY

EDITORIALS: I. How long should patients fast before surgery? Time for new guidelines..... 1
L. Strunin

II. Postoperative analgesia in children ... 4
D. Fell

ORIGINAL ARTICLES

Preoperative drinking does not affect gastric contents... 6
S. Phillips, S. Hutchinson and T. Davidson

Pain relief for infants undergoing abdominal surgery: comparison of infusions of i.v. morphine and extradural bupivacaine 10
A. R. Wolf and D. Hughes

Extra inspiratory work of breathing imposed by cricothyrotomy devices 17
R. Ooi, W. J. Fawcett, N. Soni and B. Riley

Evidence for dynamic phenomena in residual tracheal tube biofilm 22
T. J. J. Inglis

Pressure exerted by the laryngeal mask airway cuff upon the pharyngeal mucosa.. 25
R. Marjot

Comparison of the reinforced laryngeal mask airway and tracheal intubation for adenotonsillectomy 30
P. J. Williams and P. M. Bailey

Comparison of alfentanil with suxamethonium in facilitating nasotracheal intubation in day-case anaesthesia.. 34
R. Alcock, T. Peachey, M. Lynch and T. McEwan

Effect of age, gender and anaesthetic technique on the pharmacodynamics of atracurium 38
C. J. R. Parker, J. M. Hunter and S. L. Snowdon

Midazolam–alfentanil: an anaesthetic? An investigation using the isolated forearm technique.................. 42
I. F. Russell

Effects of etomidate on the adrenocortical and metabolic adaptation of the neonate.. 47
T. A. Crozier, C. Flamm, C. P. Speer, W. Rath, W. Wuttke, W. Kuhn and D. Kettler

Nitrous oxide-mediated activation of the EEG during isoflurane anaesthesia in patients...................... 54
A. Yli-Hankala, L. Lindgren, T. Porkkala and V. Jäntti

Comparison of thoracic electrical bioimpedance and thermodilution for the measurement of cardiac index in patients with severe sepsis 58
J. D. Young and P. McQuillan

Differential effects of alfentanil, fentanyl, pethidine and lignocaine administered intrathecally on nociceptive responses evoked by low and high frequency stimulation of somatic nerves.. 63
C. Wang, A. Koutsoukou-Dritsopoulou, M. K. Chakrabarti, A. Holdcroft and J. G. Whitwam

Genetic linkage analysis of chromosome 19 markers in malignant hyperthemia.. 70
S. P. Ball, H. R. Dorkins, F. R. Ellis, J. L. Hall, P. J. Halsall, P. M. Hopkins, R. F. Mueller and A. D. Stewart

In vitro effect of ephedrine, adrenaline, noradrenaline and isoprenaline on halothane-induced contractures in skeletal muscle from patients potentially susceptible to malignant hyperthermia.. 76
A. Urwyler, K. Censier, M. D. Seeberger, J. M. Rothenbühler, M. A. Kaufmann and J. Drewe

REVIEW ARTICLE

The role of recombinant growth factors in transfusion medicine.. 80
L. T. Goodnough

SHORT COMMUNICATIONS

Intra-articular morphine for pain relief after anterior cruciate ligament repair.. 87
G. P. Joshi, S. M. McCarroll, O. H. Brady, B. J. Hurson and G. Walsh

Use of alfentanil with propofol for nasotracheal intubation without neuromuscular block.................. 89
S. F. E. Coghlan, P. F. McDonald and G. Csepregi

Effect of isometric thumb preload on the evoked compound muscle action potential..................... 92
I. Kalli

Glycopyrronium prolongs topical anaesthesia of oral mucosa and enhances absorption of lignocaine 94
H. Watanabe, L. Lindgren, P. Rosenberg and T. Randell

Haemodynamic and metabolic consequences of aortic occlusion during abdominal aortic surgery............. 96
D. G. Whalley, F. C. Salevsky and J. V. Ryckman

Propofol decreases random and chemotactic stimulated locomotion of human neutrophils *in vitro*............. 99
A. G. Jensen, C. Dahlgren and C. Eintrei

CASE REPORTS

Use of transoesophageal echocardiography to manage beta-adrenoceptor block and assess left ventricular function in a patient with phaeochromocytoma 101
T. Ryan, A. Timoney and A. J. Cunningham

Use of esmolol in the postbypass management of hypertrophic obstructive cardiomyopathy.................... 104
L. G. Ooi, P. J. O'Shea and A. J. Wood

Prolonged use of isoflurane in a patient with tetanus.... 107
J. J. W. M. Stevens, R. M. Griffin and P. J. Stow

CORRESPONDENCE

Postoperative pain thresholds 110
Pharmacokinetic/pharmacodynamic modelling of atracurium 110
Sedation with propofol during regional anaesthesia...... 112
Aspirin, bleeding time and central neural block.......... 112
Death certification 112
Ketorolac postoperative analgesia......................... 112
Patient-controlled analgesia by proxy..................... 113
Veterinary use of "Xylocaine" spray 113
Use of the laryngeal mask and face mask by inexperienced personnel 114
Changes in haemodynamic variables with thiopentone, methohexitone, propofol and etomidate 115
Antepartum assessment for anaesthesia.................. 116

BOOK REVIEWS

Adult Respiratory Distress Syndrome 117
Collection d'Anesthésiologie et de Réanimation, Volume 30: Monitorage Non-Invasif en Réanimation 117
MCQs in Anaesthesia: Basic Sciences...................... 117
Key Topics in Anaesthesia 117
Moving to Audit, An Educational Package for Hospital Doctors and General Practitioners........................ 118
Hypoxia, Metabolic Acidosis and the Circulation........... 118

Erratum 119

FEBRUARY

EDITORIALS: I. Upper airway reflexes.................. 121
G. B. Drummond

II. The laryngeal mask airway in paediatric practice.......................... 124
I. G. Wilson

ORIGINAL ARTICLES

Measurement of the sensitivity of upper airway reflexes. 126
J. A. Langton, P. J. Murphy, P. Barker, A. Key and G. Smith

Effect of oral diazepam on the sensitivity of upper airway reflexes.. 131
P. J. Murphy, J. A. Langton, P. Barker and G. Smith

Logistic regression analysis of fixed patient factors for postoperative sickness: a model for risk assessment... 135
M. Palazzo and R. Evans

Comparison of automatic oscillometric arterial pressure measurement with conventional auscultatory measurement in the labour ward 141
M. A. Hasan, T. A. Thomas and C. Prys-Roberts

Use of ultrasound to evaluate internal jugular vein anatomy and to facilitate central venous cannulation in paediatric patients.................................. 145
P. J. Alderson, F. A. Burrows, L. I. Stemp and H. M. Holtby

Metabolic effects of corrective surgery in infants and children with congenital heart defects................ 149
K. Puhakka, J. Räsänen, M. Leijala and K. Peltola

Effect of nitrous oxide on cerebral blood flow in normal humans 154
L. M. Field, D. E. Dorrance, E. K. Krzeminska and L. Z. Barsoum

Neostigmine and edrophonium antagonism of moderate neuromuscular block induced by pancuronium or tubocurarine.. 160
G. D. Shorten, H. H. Ali and N. G. Goudsouzian

Tracheal intubation after induction of anaesthesia with propofol, alfentanil and i.v. lignocaine................ 163
J. A. H. Davidson and J. A. Gillespie

Effects of intradermal lignocaine and mepivacaine on human cutaneous circulation in areas with histamine-induced neurogenic inflammation..................... 167
H. Fruhstorfer and G. Wagener

Anaesthesia affects plasma concentrations of vasopressin, von Willebrand factor and coagulation factor VIII in cardiac surgical patients................................ 173
A. Kuitunen, M. Hynynen, M. Salmenperä, V. Rasi, A. Järvinen, M. Scheinin, P. J. Neuvonen and F. Fyhrquist

Effects of midazolam and flunitrazepam on the release of dopamine from rat striatum measured by *in vivo* microdialysis.. 181
K. Takada, T. Murai, T. Kanayama and N. Koshikawa

Mathematical analysis of the upper respiratory tract from an anthropometric study.............................. 186
G. Janvier, L. Bordenave, P. Revel, W. Ellison, A. M. Cros and S. Winnock

Comparison of recovery from anaesthesia induced in children with either propofol or thiopentone 192
C. J. Runcie, S. J. MacKenzie, D. S. Arthur and N. S. Morton

Acute haemodynamic effect of sodium bicarbonate in canine respiratory or metabolic acidosis 196
T. Nishikawa

Plasma concentrations of bupivacaine and its enantiomers during continuous extrapleural intercostal nerve block 201
R. G. Berrisford, S. Sabanathan, A. J. Mearns, B. J. Clarke and A. Hamdi

REVIEW ARTICLE

The haemostatic response to surgery and trauma 205
W. G. Murphy, M. J. Davies and A. Eduardo

SHORT COMMUNICATIONS

Long-term backache after extradural or general anaesthesia for manual removal of placenta: preliminary report 214
R. J. Vickers and A. E. May

Clinical evaluation of the oesophageal heat exchanger in the prevention of perioperative hypothermia........... 216
P. Kulkarni, A. Matson, J. Bright, J. Pearson and F. Carli

Effects of lorazepam on oxygen saturation before cardiac surgery 219
J. S. S. Pollock and G. N. C. Kenny

Effects of midazolam on insulin secretion from isolated rat pancreatic islets of Langerhans.................... 221
J. P. Desborough, P. M. Jones, S. J. Persaud and S. L. Howell

CASE REPORTS

Visualization of extradural blood patch for post lumbar puncture headache by magnetic resonance imaging... 223
A. G. Griffiths, S. C. Beards, A. Jackson and E. L. Horsman

Muscular paralysis and ventilatory failure caused by hyperkalaemia 226
S. J. Freeman and A. D. Fale

HISTORY

John Henry Hill Lewellin: the first etherist in Glasgow . 228
A. G. Macdonald

CORRESPONDENCE

Neuromuscular blockers in day-case surgery: is speed of onset more important than duration of action? 235
Blood loss during total hip replacement................. 235
Metabolic effects of dobutamine......................... 236
Nitrous oxide administration via oxygen therapy devices 238
Mortality in ITU patients receiving neuromuscular blocking drugs 238
Face masks and spinal anaesthesia....................... 239
Pain on i.v. injection of metoclopramide................ 239

BOOK REVIEWS

Principles and Protocols in Intensive Care 240
Conduction Blockade for Postoperative Analgesia: Mechanisms and Management 240
Techniques in Extracorporal Circulation, 3rd Edn.......... 240
Ward's Anaesthetic Equipment, 3rd Edn 241

Erratum.. 241

MARCH

EDITORIALS: I. Why not model physiologically? 243
J. W. Sear

II. Synergy and isoboles.................. 246
T. N. Calvey

ORIGINAL ARTICLES

A physiological model for the distribution of injected agents, with special reference to pethidine............ 248
N. R. Davis and W. W. Mapleson

Effect on lung volumes of oxygen concentration when breathing is restricted 259
A. B. Baker, A. McGinn and C. Joyce

Effects of PEEP on dynamic hyperinflation in patients with airflow limitation.................................. 267
I. K. S. Tan, S. B. Bhatt, Y. H. Tam and T. E. Oh

Minimum alveolar concentration of sevoflurane in elderly patients 273
R. Nakajima, Y. Nakajima and K. Ikeda

Clinical and radiological comparison of perivascular and transarterial techniques of axillary brachial plexus block 276
P. Pere, M. Pitkänen, M. Tuominen, J. Edgren and P. H. Rosenberg

Improvement in i.v. regional anaesthesia by re-exsaguination before surgery.................................... 280
N. Rawal, J. Hallén, A. Amilon and P. Hellstrand

Pharmacokinetics of flumazenil and midazolam.......... 286
R. D. M. Jones, K. Chan, C. J. Roulson, A. G. Brown, I. D. Smith and G. H. Mya

Diclofenac and ketoprofen for pain treatment after elective Caesarean section 293
M. G. F. Rorarius, P. Suominen, G. A. Baer, O. Romppanen and R. Tuimala

Preoperative indomethacin for pain relief after thoracotomy: comparison with postoperative indomethacin 298
D. F. Murphy and C. Medley

Effects of surgical stimulation on autonomic reflex function: assessment by changes in heart rate variability 301
T. W. Latson and D. O'Flaherty

Haemodynamic and catecholamine responses to induction of anaesthesia and tracheal intubation: comparison between propofol and thiopentone........ 306
L. Lindgren, A. Yli-Hankala, T. Randell, M. Kirvelä, M. Scheinin and P. J. Neuvonen

Plasma catecholamines and neonatal condition after induction of anaesthesia with propofol or thiopentone at Caesarean section 311
T. Gin, M. E. O'Meara, A. F. Kan, R. K. W. Leung, P. Tan and G. Yau

Benzodiazepines and their solvents influence neutrophil granulocyte function 317
M. Weiss, N. Mirow, A. Birkhahn, M. Schneider and P. Wernet

Platelet serotonin is a mediator potentially involved in anaphylactic reaction to neuromuscular blocking drugs 322
N. Bermejo, J. L. Guéant, E. Mata, P. Gérard, D. A. Moneret-Vautrin and M. C. Laxenaire

I.v. bolus administration of subconvulsive doses of lignocaine to conscious sheep: myocardial pharmacokinetics... 326
Y. F. Huang, R. N. Upton and W. B. Runciman

Influence of cardiac output, injection time and injection volume on the initial mixing of drugs with venous blood after i.v. bolus administration to sheep 333
R. N. Upton and Y. F. Huang

REVIEW ARTICLES

Hepatotoxicity of volatile anaesthetics 339
R. H. Elliott and L. Strunin

Perioperative management of the obese patient.......... 349
Z. Shenkman, Y. Shir and J. B. Brodsky

SHORT COMMUNICATIONS

Studies of gastric content: comparison of two methods. 360
E. Søreide, J. A. Søreide, H. Holst-Larsen and P. A. Steen

Accumulation of acetone in blood during long-term anaesthesia with closed systems 363
J. M. Strauß and J. Hausdörfer

Test-tube equilibration of volatile anaesthetic concentrations.. 365
D. C. Martin, J. K. Pruett and R. S. Aronstam

CASE REPORTS

Delayed presentation of an extradural abscess in a patient with alcohol abuse 368
O. Nordström and R. Sandin

Electrode burns during local hyperthermia............... 370
D. G. Stott and W. A. Wallbank

APPARATUS

Comparison of portable emergency ventilators using a lung model 372
L. Attebo, M. Bengtsson and A. Johnson

CORRESPONDENCE

Pre-emptive analgesia..................................... 378
Effect of nitrous oxide on auditory evoked potentials ... 379
Use of lignocaine in ventricular defibrillation?........... 380
Regurgitation and the laryngeal mask airway............ 380
Explaining risk to patients................................ 381
Editorial II—the National Confidential Enquiry into Perioperative Deaths 382
Bacterial retention properties of heat and moisture exchange filters 382
Propofol and alfentanil mixture.......................... 382
Different rates of injection of propofol 383
Subdural catheterization and cord damage............... 384
Frequency of damaged coaxial breathing systems........ 384

BOOK REVIEWS

Hyperalgesia and Allodynia 385
Medical Writing: A Prescription for Clarity................ 385
Anaesthesia Review 385

APRIL

EDITORIAL: Extradural abscess after central neural block 387
J. A. W. Wildsmith

ORIGINAL ARTICLES

Closed-loop feedback controlled administration of alfentanil during alfentanil–nitrous oxide anaesthesia 389
H. Schwilden and H. Stoeckel

Comparison of the effect of EMLA cream, subcutaneous ring anaesthesia and a double cuff technique in the prevention of tourniquet pain 394
Y.-C. Tsai, Y.-Y. Lai and C.-L. Chang

Comparison of *in vitro* contracture testing with ryanodine, halothane and caffeine in malignant hyperthermia and other neuromuscular disorders 397
P. M. Hopkins, F. R. Ellis and P. J. Halsall

Recoveries of post-tetanic twitch and train-of-four responses after administration of vecuronium with different inhalation anaesthetics and neuroleptanaesthesia... 402
Y. Saitoh, H. Toyooka and K. Amaha

Prejunctional action of neostigmine on mouse neuromuscular preparations.................................. 405
M. F. M. Braga, E. G. Rowan, A. L. Harvey and W. C. Bowman

An alternative method of increasing $P\text{CO}_2$ using apnoea and continuous positive airway pressure 411
R. Karlsten and S. Englesson

Ventilatory effects of morphine, pethidine and methadone in children................................ 414
K. Hamunen

Comparison of midazolam with propofol for sedation in outpatient bronchoscopy 419
M. Crawford, J. Pollock, K. Anderson, R. J. Glavin, D. MacIntyre and D. Vernon

Comparison of infusion rates of three i.v. anaesthetic agents for induction in elderly patients 423
M. C. Berthoud, G. A. McLaughlan, I. J. Broome, P. D. Henderson, J. E. Peacock and C. S. Reilly

Haemodynamic changes produced by inhalation anaesthetics in the presence of phosphodiesterase inhibition 428
G. Molter, R. Larsen, U. Peters, U. Bauch and R. Sefrin

REVIEW ARTICLE

The value of pre-emptive analgesia in the treatment of postoperative pain 434
J. B. Dahl and H. Kehlet

SHORT COMMUNICATIONS

Comparison of nasal cannulae with face mask for oxygen administration to postoperative patients 440
K. M. Nolan, J. A. Winyard and D. R. Goldhill

Relationship between volume of distribution of atracurium and body weight 443
C. J. R. Parker and J. M. Hunter

Pipecuronium-induced prolongation of vecuronium neuromuscular block 446
I. Smith and P. F. White

Effect of radiant heat on the metabolic coat of postoperative shivering 449
A. Sharkey, R. H. Gulden, J. M. Lipton and A. H. Giesecke

Metabolic effects of propofol and flunitrazepam given for sedation after aortic surgery 451
F. Moritz, J. Petit, N. Kaeffer, G. Oksenhendler, H. Papion, B. Hecketsweiler, N. Moore and C. Winckler

Hepatic elimination of diazepam: interactions with albumin, desflurane and sevoflurane 454
O. Dale, E. J. Frink, L. Thommesen and A. J. Gandolfi

Anaesthetic properties of dimethylthiourea 456
D. D. Koblin, M. J. Laster and J. Liu

CASE REPORTS

Spontaneous excitatory movements during recovery from propofol anaesthesia in an infant: EEG evaluation 459
A. Borgeat, O. H. G. Wilder-Smith, P. A. Despland and P. Ravussin

A continuous subdural block 462
C. B. Collier, S. P. Gatt and S. M. Lockley

Possible venous air embolism with a new water jet dissector 466
J. A. S. Smith

APPARATUS

Fresh gas requirements of an enclosed afferent reservoir breathing system in anaesthetized, spontaneously breathing adults 468
J. R. Barrie, P. C. W. Beatty, I. T. Campbell, G. Meakin and T. E. J. Healy

COMMENTARY

Spinal extradural abscess: pursuit of vigilance 471
P. R. Bromage

ABSTRACTS

Proceedings of the Anaesthetic Research Society, London Meeting, November 20–21, 1992 .... 474P

CORRESPONDENCE

Lumbovertebral syndrome after extradural blood patch . 489
Intermittent *vs* continuous extradural infusion of bupivacaine during labour 490
Does etomidate cause haemolysis? 490
Xylometazoline and porphyria 491
Transthoracic endoscopic sympathectomy 491
Perioperative blood loss 492
Pre-emptive extradural analgesia 493
Metabolic effects of cholecystectomy 493

BOOK REVIEWS

ABC of Transfusion, 2nd Edn 495
British Medical Bulletin: A Series of Expert Reviews. Pain, Mechanisms and Management 495
Specialty Medical Audit (Medical Audit Series 4) 495
Management of Acute Pain: A Practical Guide 495

Erratum 494

MAY

EDITORIAL: Double-lumen tubes 497
R. S. Vaughan

ORIGINAL ARTICLES

Continuous spirometry for detection of double-lumen endobronchial tube displacement 499
G. I. Bardoczky, M. Levarlet, E. Engelman and P. deFrancquen

Patient-controlled extradural analgesia to compare bupivacaine, fentanyl and bupivacaine with fentanyl in the treatment of postoperative pain 503
D. W. Cooper and G. Turner

Efficacy of continuous intercostal bupivacaine for pain relief after thoracotomy 508
C. M. Dryden, I. McMenemin and D. J. R. Duthie

Morphine-6-glucuronide disposition in renal impairment 511
M. H. Hanna, F. D'Costa, S. J. Peat, C. Fung, N. Venkat, T. R. Zilkha and S. Davies

Partial reversal of the effects of extradural clonidine by oral yohimbine in postoperative patients 515
N. Liu, F. Bonnet, L. Delaunay, N. Kermarec and G. D'Honneur

The pressor response to venous cannulation: attenuation by prior infiltration with local anaesthetic 519
B. T. Langham and D. A. Harrison

Surfactant and adult respiratory distress syndrome 522
W. Jacobson, G. R. Park, T. Saich and J. Holcroft

Penetration of an aerosol, produced by film atomization, through the carinal bifurcation 527
T. J. J. Inglis, J. G. Jones and S. Paxton

Effect of hyperoxia on the breathing of patients anaesthetized with infusions of propofol 532
A. C. Dow and N. W. Goodman

Effects of active and passive sighs in normoxia and hyperoxia on the breathing of patients anaesthetized with infusions of propofol 536
N. W. Goodman and A. C. Dow

I.v. anaesthesia with propofol using a target-controlled infusion system: comparison with inhalation anaesthesia for general surgical procedures in children ... 542
E. Doyle, W. McFadzean and N. S. Morton

Pharmacokinetics of propofol administered by infusion in dogs undergoing surgery 546
A. Nolan and J. Reid

In vivo determination of concentration–effect curves of local anaesthetics in man 552
R. Wiesemes, W. Klement, G. E. K. Novotny and P. Lipfert

I.v. bolus administration of subconvulsive doses of lignocaine to conscious sheep: relationships between myocardial pharmacokinetics and pharmacodynamics. 556
Y. F. Huang, R. N. Upton and W. B. Runciman

REVIEW ARTICLE

The management of acute poisoning 562
G. G. Collee and G. C. Hanson

SHORT COMMUNICATIONS

Effect of age on the sensitivity of upper airway reflexes . 574
R. J. Erskine, P. J. Murphy, J. A. Langton and G. Smith

Endobronchial cuff pressures 576
M. Cobley, J. F. Kidd, B. A. Willis and R. S. Vaughan

Lipid solubility of pancuronium and vecuronium determined by n-octanol/water partitioning 579
M. Weindlmayr-Goettel, H. Gilly, E. Sipos and K. Steinbereithner

Tetanic fade during recovery from vecuronium block: comparison of systemic and isolated forearm administration 581
N. T. A. Campkin, J. R. Hood and S. A. Feldman

CASE REPORTS

Adult respiratory distress syndrome after attempted strangulation 583
P. G. Murphy, R. Jackson, R. Kirollos, J. S. Gibson and P. Chennells

Anaesthetic implications of the anti-cardiolipin antibody syndrome 587
G. Menon and J. Allt-Graham

Spontaneous reposition of a dislocated arytenoid cartilage 591
A. Gauss, H. S. Treiber, J. Haehnel and H. S. Johannsen

CORRESPONDENCE

"Concorde nose" in Whitacre spinal needles 593
Peripheral nerve damage and regional anaesthesia 593
Statistical assessment of two methods of clinical measurement 595
Cricoid pressure and the laryngeal mask airway 596
Laparoscopic *vs* open cholecystectomy 597
Combined caffeine–halothane test for malignant hyperthermia 597
Spin resonance spectroscopy to detect malignant hyperthermia susceptibility 598
The airway decides the anaesthetic approach before tracheal intubation 600
Pain relief after anterior cruciate ligament repair 600

BOOK REVIEWS

The Oxford Textbook of Clinical Pharmacology and Drug Therapy, 2nd Edn 601
Handbook of Percutaneous Central Venous Catheterisation, 2nd Edn 601
Electrical Trauma: the Pathophysiology, Manifestations and Clinical Management 601

JUNE

EDITORIAL: IVOX 603
J. Skoyles and M. Pepperman

ORIGINAL ARTICLES

Components of the inspiratory–arterial isoflurane partial pressure difference 605
M. J. Landon, A. M. Matson, B. D. Royston, A. M. Hewlett, D. C. White and J. F. Nunn

Comparison of the sedative and amnesic effects of midazolam and propofol 612
M. R. Polster, P. A. Gray, G. O'Sullivan, R. A. McCarthy and G. R. Park

Plasma concentrations of midazolam after i.v., nasal or rectal administration in children 617
J.-M. Malinovsky, C. Lejus, F. Servin, J.-Y. Lepage, Y. Le Normand, S. Testa, A. Cozian and M. Pinaud

Transoesophageal echocardiographic assessment of haemodynamic function during laparoscopic cholecystectomy 621
A. J. Cunningham, J. Turner, S. Rosenbaum and T. Rafferty

Efficacy of postoperative pain treatment regimens using both buprenorphine and papaveretum sequentially after abdominal hysterectomy 626
D. W. Green, L O'Connor and M. Hanna

Evaluation of the analgesic effect of metoclopramide after opioid-free analgesia 631
B. Lisander

Incremental spinal anaesthesia for elective Caesarean section: maternal and fetal haemodynamic effects 634
S. C. Robson, G. Samsoon, R. J. Boys, C. Rodeck and B. Morgan

Spread of spinal anaesthesia for Caesarean section in singleton and twin pregnancies 639
B. Jawan, J. H. Lee, Z. K. Chong and C. S. Chang

Direct spinal effect of intrathecal and extradural midazolam on visceral noxious stimulation in rabbits 642
M. E. Crawford, F. Molke Jensen, D. B. Toftdahl and J. B. Madsen

Cardiovascular effects of i.v. induction in children: comparison between propofol and thiopentone 647
C. S. T. Aun, R. Y. T. Sung, M. E. O'Meara, T. G. Short and T. E. Oh

Effect of extradural analgesia on stress responses to abdominal surgery in infants 654
A. R. Wolf, R. L. Eyres, P. C. Laussen, J. Edwards, I. J. Stanley, P. Rowe and L. Simon

Volume replacement with hydroxyethyl starch solution in children 661
J. Boldt, C. Knothe, E. Schindler, H. Hammermann, F. Dapper and G. Hempelmann

Pharmacokinetics and pharmacodynamics of ketamine enantiomers in surgical patients using a stereoselective analytical method 666
G. Geisslinger, W. Hering, P. Thomann, R. Knoll, H.-D. Kamp and K. Brune

REVIEW ARTICLE

Prevention and treatment of hypotension during central neural block 672
A. F. McCrae and J. A. W. Wildsmith

SHORT COMMUNICATIONS

Haemodynamic changes in patients undergoing laparoscopic cholecystectomy: measurement by transthoracic electrical bioimpedance 681
L. A. H. Critchley, J. A. J. H. Critchley and T. Gin

Alterations in pain threshold and psychomotor response associated with subanaesthetic concentrations of inhalation anaesthetics in humans 684
K. Tomi, T. Mashimo, C. Tashiro, M. Yagi, M. Pak, S. Nishimura, M. Nishimura and I. Yoshiya

Adrenaline-induced hypotension in neurosurgery 687
S. Phillips, S. E. Hutchinson, P. Bayly and T. E. Hollway

Shunt flow and caval pressure gradient during veno–venous bypass in human orthotopic liver transplantation 689
R. U. Scherer, R. M. Giebler, M. J. Schmutzler, F. M. Günnicker and W. J. Kox

Tracheal tube cuff inflation as an aid to blind nasotracheal intubation 691
A. C. Van Elstraete, J. H. Pennant, N. M. Gajraj and R. A. Victory

Potency estimation of mivacurium: comparison of two different modes of nerve stimulation 694
V. R. Maddineni, R. K. Mirakhur, R. Cooper and E. McCoy

CASE REPORT

A bifurcated endobronchial tube in the management of laryngotracheo-oesophageal cleft repair 698
R. Ahmad, K. A. Sami and A. Rabeeah

CORRESPONDENCE

Haemostasis and thrombelastography: a cautious note .. 699
Continuous subarachnoid infusion of 0.125% bupivacaine for analgesia during labour 700
Preoperative drinking and gastric contents 701
Extradural abscess in the postpartum period 703
The laryngeal mask and intraocular surgery 704
Brain partial pressure of isoflurane and nitrous oxide ... 704
Hypertonic solutions in massive haemorrhage 705
Metal particle generation caused by the combined spinal–extradural technique 706
Fractional utilization of fresh gas by breathing systems without carbon dioxide absorption 706

BOOK REVIEWS

Anesthésie et Analgésie en Obstétrique. Collection d'Anesthésiologie et de Réanimation, Vol. 33 708
Transesophageal Echocardiography 708
The Complete Recovery Room Book 709
Essay Plans for Anaesthesia Exams 709

Errata 710

Index to Volume 70 711

SUPPLEMENT

THE EUROPEAN SOCIETY FOR ANAESTHESIOLOGISTS - FOUNDING ESA MEETING

Epidemiology in anaesthesia and intensive care A.1–A.8
Outpatient anaesthesia A.9–A.14
Patient safety, equipment, monitoring and computers A.15–A.20
Clinical circulation: Transoesophageal echocardiography, myocardial ischaemia detection A.21–A.26
Clinical circulation: Anaesthesia and intensive care related to cardiac surgery A.27–A.31
Clinical circulation: General A.32–A.43
Experimental circulation A.44–A.52
Respiration A.53–A.68
Metabolism, nutrition, endocrinology: Thermoregulation A.69–A.74
Metabolism, nutrition, endocrinology: Anaesthesia and transplantation A.75–A.85
Metabolism: General A.86–A.96
Clinical circulation: Blood preservation A.97–A.104
Neurosciences A.105–A.119
Local and regional anaesthesia A.120–A.132
Pharmacology: Neuromuscular blockers A.133–A.142
Pharmacology: General A.143–A.157
Paediatric anaesthesia and intensive care A.158–A.168
Obstetric anaesthesia A.169–A.177
Intensive care medicine A.178–A.191
Resuscitation and emergency medicine A.192–A.197
Acute and chronic pain management A.198–A.213

Papers for publication and all editorial communications should be addressed to:
Professor G. Smith,
Editor, British Journal of Anaesthesia,
University Department of Anaesthesia,
Leicester Royal Infirmary,
Leicester LE1 5WW.
Telephone: 0533 470141
Fax: 0533 854487

All **business communications** should be sent to the Publishers: Professional & Scientific Publications Ltd, BMA House, Tavistock Square, London WC1H 9JR.

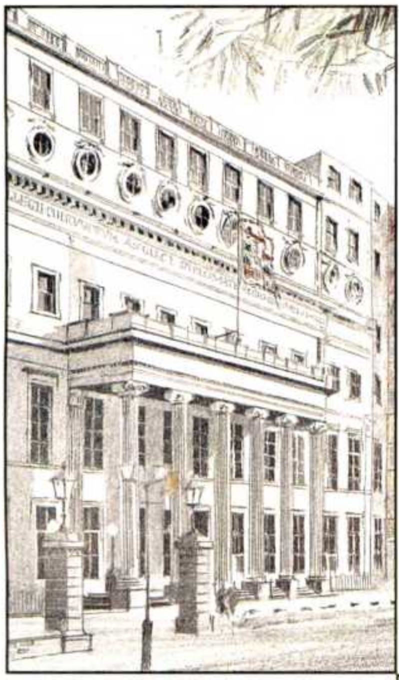
The GUIDE TO CONTRIBUTORS may be found in the advertisement section of this issue (pages ii, iv & vi).
Published monthly. Annual subscriptions: Worldwide £125.00; USA only $198.00 (direct orders only). Trainee rate: Worldwide £69.00. Airmail rates on application. ISSN 0007–0912. Orders must be accompanied by payment; cheques should be made payable to Professional and Scientific Publications. Orders and payments should be sent to Professional and Scientific Publications, BMA House, Tavistock Square, London WC1H 9JR. Orders in the United States of America may be sent to Professional and Scientific Publications, Box 560B, Kennebunkport, Maine 04046.

Group Advertisement Director, Mr R. Hayzen.
Advertisement Manager, Mr A. Allsop.
Production Manager, Mr D. Shaw.
BMA House, Tavistock Square, London WC1H 9JR. 071-387 4499.

Whilst every effort is made by the publishers and editorial committee to see that no inaccurate or misleading data, opinions or statement appear in this Journal, they wish to make it clear that the data and opinions appearing in the articles and advertisements herein are the responsibility of the contributor or advertiser concerned. Accordingly, the publishers and the editorial committee and their respective employees, officers and agents accept no liability whatsoever for the consequences of any such inaccurate or misleading data, opinions or statements. Whilst every effort is made to ensure that drug doses and other quantities are presented accurately, readers are advised that new methods and techniques involving drug usage, and described within this Journal, should only be followed in conjunction with the drug manufacturer's own published literature.

© Copyright: 1993 *British Journal of Anaesthesia*
All rights reserved. No part of this publication may be reproduced, stored in a retrieval system, or transmitted in any form by any means, electronic, mechanical, photocopying, recording or otherwise, without the prior permission of the *British Journal of Anaesthesia*, requests for which should be addressed to the **Editor**.

Published by Professional and Scientific Publications.
Printed in Great Britain by the University Press, Cambridge.



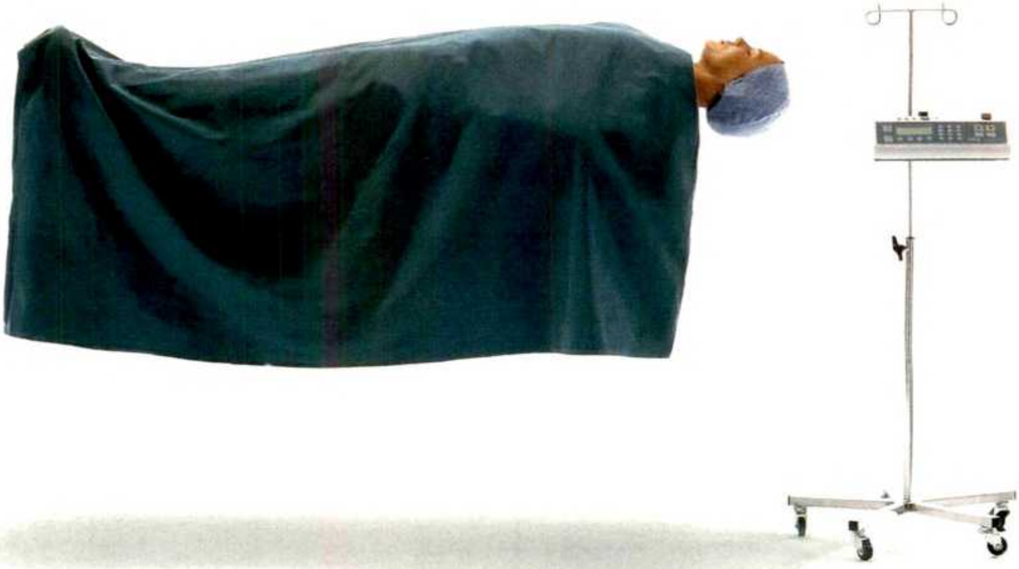
THE ROYAL COLLEGE OF ANAESTHETISTS NEWSLETTER

GOLDEN JUBILEE YEAR

No. 39 March 1998 *Supplement*

ZP117

Diprivan 1%
propofol
MAINTENANCE



Easily controllable anaesthesia[1, 2] and good recovery characteristics[3]
are the hallmarks of maintenance with 'Diprivan'

Diprivan 1%
propofol
MAINTENANCE
Furthering
the art of
anaesthesia

PRESCRIBING NOTES
'DIPRIVAN' 1%
Consult Data Sheet before prescribing.
USE Induction and maintenance of general anaesthesia. Sedation of ventilated patients receiving intensive care for up to three days. Sedation for surgical and diagnostic procedures.
PRESENTATION Ready to use, isotonic, aqueous emulsion containing 10mg/ml propofol in a vehicle containing soybean oil and purified egg phosphatide.
DOSAGE AND ADMINISTRATION Induction: Titrate against response. Adults: Approximately 4ml every 10 seconds in healthy patients and 2ml every 10 seconds in patients of ASA grades 3 and 4. Patients under 55 years are likely to require 1.5 to 2.5mg/kg; older patients generally require less. Children over 8 years: Usually approximately 2.5mg/kg; children 3-8 years may require more. Lower dosage in patients of ASA grades 3 and 4. Children under 3 years: not recommended.
Maintenance: Titrate against response. Adults: Usually 4 to 12mg/kg/hr. Alternatively repeat bolus injections of 25mg to 50mg (2.5 to 5.0ml) may be administered according to clinical need. Children over 3 years: Usually 9 to 15mg/kg/hr. Children under 3 years: not recommended.
Sedation during intensive care: Adults: 0.3 to 4.0mg/kg/hr by continuous infusion. Rates greater than 4mg/kg/hr are not recommended. Take account of other lipids being given. Monitor blood lipid levels of patients at risk of fat overload. Children: not recommended (see Data Sheet).
Sedation for surgical and diagnostic procedures: Adults: 0.5 to 1.0mg/kg over 1 to 5 minutes for onset of sedation. 1.5 to 4.5mg/kg/hr for maintenance of sedation. Bolus administration of 10 to 20mg for rapid increase in depth of sedation. Children: not recommended.
CONTRA-INDICATIONS, WARNINGS, ETC. Contra-indicated in allergy to 'Diprivan' 1%. Not recommended in ECT. Do not use in pregnancy or for obstetric anaesthesia. Should be given only by those trained in anaesthesia or intensive care. Facilities for maintenance of airway, artificial ventilation and oxygen enrichment should be available. 'Diprivan' 1% should not be administered by the person conducting the diagnostic or surgical procedure. Monitor for early signs of hypotension, airway obstruction and oxygen desaturation during sedation. Patients should avoid alcohol before and for 8 hours after administration. Caution when used to sedate patients undergoing procedures where spontaneous movements are undesirable. Extreme caution during bolus administration in acute pulmonary insufficiency or respiratory depression. Concomitant use with CNS depressants, general anaesthetics and narcotic analgesics will accentuate sedative effects. Severe respiratory and cardiovascular depression may occur when combined with parenteral CNS depressants. Caution in cardiac, respiratory, renal or hepatic impairment, in hypovolaemic, elderly or debilitated patients and in disorders of fat metabolism or conditions where lipid emulsions should be used cautiously. Hypotension and transient apnoea may occur during induction. The risk of relative vagal overactivity may be increased, associated with bradycardia and asystole; consider administration of anticholinergic agent before induction or during maintenance when vagal tone is dominant. There may be a risk of convulsion in epileptic patients. Sexual disinhibition may occur during recovery. Safety in breast feeding not established. Ability to drive or operate machinery may be affected. An adequate period is needed prior to discharge to ensure full recovery.
'Diprivan' 1% contains no antimicrobial preservative and supports the growth of microorganisms. Administration must commence without delay after opening the container. Maintain asepsis for 'Diprivan' 1% and all infusion equipment.
'Diprivan' 1% and any equipment is for single use in an individual patient. Discard and replace infusion lines and reservoirs of 'Diprivan' 1% at regular intervals during long-term maintenance or sedation in intensive care. Do not mix prior to administration with other agents or infusion fluids except 5% Dextrose. Do not administer via a microbiological filter.
SIDE EFFECTS Convulsions, myoclonus and opisthotonos may occur (occasionally delayed). Spontaneous movements and pulmonary oedema have been observed. Nausea, vomiting and headache in a small proportion of patients. Rarely, clinical features of anaphylaxis, which may include angioedema, bronchospasm, erythema and hypotension, have been reported with 'Diprivan' 1%. Pain on injection in a proportion of patients. Discolouration of urine and venous sequelae are rare. Post-operative fever has been reported. Minimal evidence of excitation on induction.
LEGAL CATEGORY POM.
PRODUCT LICENCE NUMBER 12619/0010.
BASIC NHS COST £3.88 per 20ml ampoule, £9.70 per 50ml infusion vial, £19.40 per 100ml infusion vial.
'Diprivan' is a trademark, the property of Zeneca Limited.
Further information is available from: ZENECA Pharma, King's Court, Water Lane, Wilmslow, Cheshire SK9 5AZ.
References: **1.** White M, Kenny GNC. Anaesthesia 1990; **45:** 204-209. **2.** Steegers PA and Foster PA. Anaesthesia 1988; **43**(Suppl): 94-97. **3.** DeGrood PMRM, Harbers JBM, Van Egmond J, Crul JF. Anaesthesia 1987; **42:** 815-823.

ZENECA

96/5243/KK/Issued Jan '98

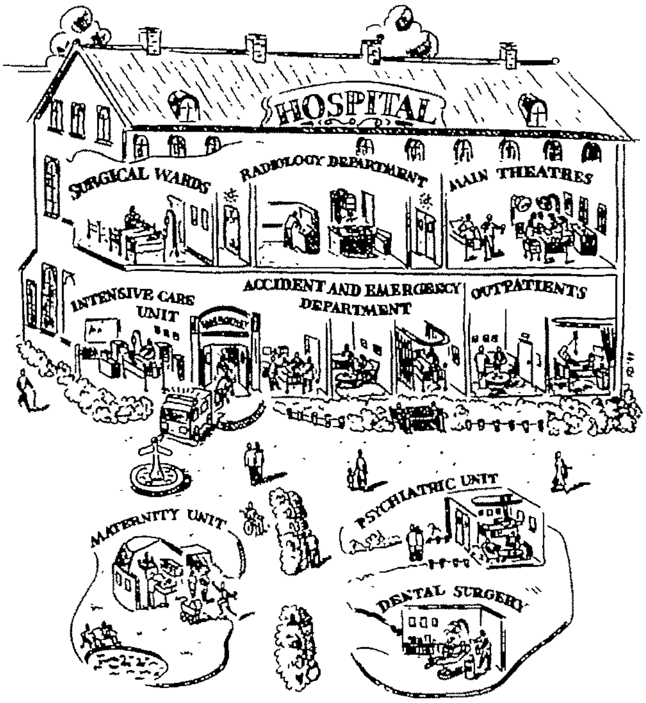
ZENECA

This publication is supported by an educational grant from Zeneca Pharma

President's Statement

It is a common assumption that the Royal College of Anaesthetists (RCA) has as its primary concern trainee anaesthetists. This is true, but there is also a clear responsibility of the RCA for all others engaged in anaesthetic practice, including the non-consultant and consultant career grades. This way always assumed to be one of the powers of our Royal Charter, but this is not strictly speaking a statutory instrument. However, there are now legal powers laid down for the RCA in the European Specialist Qualifications Medical Order 1995 and the amendments for non-consultant career grade doctors in 1997. Furthermore, the General Medical Council has made it clear in its recent documents that we are all responsible for each other and that the Royal Colleges have a clear role in this matter. In addition, a number of documents have been published and events have occurred recently which impinge on this area of the RCA's interest and influence. These include the White Paper on the National Health Service (NHS), the Audit Commission Report on Anaesthetic Services, and the deliberations of the Specialty Workforce Advisory Group (SWAG - a sub-Committee of the Advisory Group (AGMETS) to the Department of Health) which determines how many SpR posts by specialty there should be in the coming year. This President's Statement will explore some of the interactions of this material, which I hope will be of interest to Fellows and Members.

The Audit Commission Report published in December 1997 is an excellent overview of anaesthesia services (excluding Intensive Care Medicine - the subject of a current review) in the National Health Service. The Report illustrates the pivotal role of anaesthesia in the running of acute service hospitals and contains much material which anaesthetic departments should use to persuade their administrations to improve services to the standard of the best described in the report. The figure from the Report (published with the permission of The Audit Commission) accompanying this article shows in diagrammatic form that anaesthesia pervades all aspects of an acute hospital. Indeed it could form part of a quiz - asking the question "what's missing?" - answer: "the considerable administrative role of anaesthetic departments in day surgery, operating theatres and recovery units, high dependency units, intensive care units and resuscitation services".



One item in the Report which received undue publicity was the impression that there is a shortage of anaesthetists. The Audit Commission did not conduct a manpower survey but conducted a rather biased questionnaire of Chief Executives of Trusts who responded on their past experience when there was difficulty in filling consultant posts. All the evidence we have from our own RCA manpower database and that run by SWAG indicates that over the next four years there will be no shortage of qualified trainees with their CCST ready for consultant posts. Indeed, if consultant expansion is less than 5% per annum (the figure used for prediction of manpower requirements in anaesthesia for the future) there is a risk of overproduction. This would clearly be unsatisfactory. The proposal to extend the SpR period from four years to five (recommended by Council in November 1997 - to begin in January 1999 to accommodate all our training requirements and the proposed further reduction in trainee hours) will help to stem excess production. Nevertheless, we may still need to reduce SpR positions as is currently being recommended by SWAG. The dilemma is that there still are hospitals, including some of our large teaching hospitals, which do not have sufficient consultants and are having great difficulty in fulfilling their service and training requirements. In addition, these are often the very hospitals without the financial resources to advertise consultant posts at a time when there are suitable candidates. Any reduction in SpR positions for these hospitals, without consultant expansion, may be detrimental to the point where they can no longer meet the RCA training requirements. The RCA is engaged in close consultations with the Department of Health as to how these two apparently opposing forces can be reconciled.

The White Paper on the National Health Service commits the service to quality issues. Once way of doing this is the proposal to establish a National Institute for Clinical Excellence (NICE). How this will function is still to be determined. It is of interest, however, that anaesthesia is already considering this matter. Last year all specialties were summoned to a meeting with the Chief Medical Officer to address the problem of outcome studies and improving quality in all specialties. The RCA and the Association of Anaesthetists of Great Britain and Ireland (AAGBI) were asked jointly to put forward a proposal on behalf of anaesthesia for 1998. The exercise is being run by the Joint Consultants Committee (JCC) and the Academy of Medical Royal Colleges (AMRC). The RCA and AAGBI set up a working group Chaired by Dr John Searle which is already well on in its deliberations.

A simple outcome indicator was not thought to be relevant for anaesthesia. Instead the concept of bench marks of good practice we could all agree to, and how to achieve these and how to help those who were having difficulties was thought to be more appropriate. The group is, therefore developing, a "Good Practice Guide for Anaesthesia". It is out intention to hold a meeting of all Clinical Directors in July 1998 to present this Guide in a workshop form. This will be a unique event. At one time and place all those with senior responsibility for NHS anaesthetic services will be able to help the RCA and AAGBI produce a document which all anaesthetists can use to ensure that their practice meets the high standards we all aspire to. In addition, the Guide will be available to all others as evidence of our commitment to quality in our activities.

Anaesthetists sometimes show paranoid tendencies in a belief that nobody knows who we are and what we do or appreciates our contributions to the NHS. I hope that the matters discussed in this statement will go a little way to dispelling these delusions. Make no mistake the senior players in the Department of Health are well aware of the importance of anaesthesia in maintaining the acute sectors of the NHS. The Audit Commission Report has a wealth of material in it illustrating how vital anaesthesia is and it is now up to anaesthetic departments to ensure that as the actual Audit takes place during 1998 they take full advantage to influence their respective Trusts and future "purchasers". For example, by the end of the year every Trust could have an effective postoperative pain service run by anaesthesia; the "Cinderella" of obstetric anaesthesia could be resolved; and the out of hours "emergency work" could be under control. The Audit Commission has provided the tools, it's now up to us to make it happen.

Leo Strunin, President.

THE ROYAL COLLEGE OF ANAESTHETISTS
48/49 RUSSELL SQUARE
LONDON WC1B 4JY
Tel: 0171 813 1900
Fax: 0171 813 1876
website: http://www.rcoa.ac.uk

President:
Professor L Strunin (London)

Vice-Presidents:
Dr S M Willatts (Bristol)
Dr W R MacRae (Edinburgh)

Chief Executive:
Ms W Cogger

Registrar:
Dr J M Davies

Editor:
Professor J G Jones (Cambridge)

CONTENTS

President's Statement
page 1-2

Editorial
page 3-4

From the Registrar
page 5

The Evolution of the Faculty of Anaesthetists of the Royal College of Surgeons
page 6-9

A Physicist in Anaesthesia
page 9-11

Drug Dependence Among Anaesthetists in the United States
page 12-15

What is the Future of CME?
page 15, 18-19

PERSONAL VIEW 1:
James Rochford 1915-1979
page 19-20

PERSONAL VIEW 2:
How Could a Course Taking Place in a Remote Corner of Uganda be so Important?
page 20-21

Correspondence
page 22-25

Editorial

Looking Backwards, Looking Forwards

The foundation of the Faculty of Anaesthetists 50 years ago occurred at a time of enormous change in British Medicine and in Anaesthesia itself. Three years after the end of the Second World War the country was in the throes of widespread nationalisation under a newly elected Labour Government but the country was bankrupt and almost every commodity was rationed and in short supply.

Coinciding with the start of the National Health Service was the end of the era where inhalation anaesthesia with spontaneous breathing was used almost exclusively. Enormous changes were being introduced to anaesthetic practice as a result of the rapidly increasing use of intravenous anaesthesia with thiopentone and neuromuscular blockade with curare. Until that time anaesthetics were administered by an assortment of hospital doctors, general practitioners, dentists and nursing sisters. Even before the 1940's "death on the table" was not a rare complication of general anaesthesia, some practitioners being associated with many more deaths than others. Not only was the specialty suddenly in need of re-invention, there was also an urgent need for the development of an understanding of the dangers of the two new intravenous drugs. The Association of Anaesthetists, already in existence, was one of the bodies that saw the need for a Faculty or College of Anaesthetists to oversee the standards in the specialty. In this issue Professor Cecil Gray describes the foundation and evolution of the Faculty of Anaesthetists.

The 50 years which followed the introduction of the Health Service and Faculty/College of Anaesthetists saw the rapid development of a hardware-orientated specialty. The anaesthetist by and large had to be a mechanically minded person. Most were keen to advance his/her practice by developing the educated hand

Articles and correspondence for inclusion in the May issue should be sent to the Editor (c/o Mrs M J Kelly at the College) by Friday, 20 March 1998.

©Royal College of Anaesthetists Newsletter 1998
All Rights Reserved. No part of this publication may be reproduced, stored in a retrieval system, or transmitted in any form or by any other means, electronic, mechanical, photocopying, recording, or otherwise, without prior permission, in writing, of the Royal College of Anaesthetists.

and inventing all kinds of needles, tubes, connectors airways, masks, vaporisers, ventilators and later blood gas analysers and monitoring equipment. Many of these devices developed in the 1950's and 60's were the results of the efforts of anaesthetists themselves. Some, such as the Manley Ventilator, are still in use in my hospital today. In this issue John Bushman describes some of the work of another innovator James Rochford, and Bill Mapleson outlines some of his own work over most of the last 50 years. In parallel with all these changes were a number of spectacular advances made by pharmaceutical companies. In particular the introduction of new volatile and intravenous anaesthetic agents, opioids as well as a range of muscle relaxants. Against this background the Faculty/College introduced the FFARCS/FRCA examination as well as many courses and became increasingly concerned with standards of anaesthetic training and practice. With all these developments Anaesthesia spawned a number of promising offspring. Particularly notable were intensive care and chronic pain therapy. Both subspecialties began tackling problems in which initially no one else wanted to get involved but now, after much of the heavy spadework has been done by anaesthetists, both seem ripe for cherry picking by other specialties and may split from the parent specialty.

What of the specialty of anaesthesia itself now and in the future? 50 years after the introduction of the National Health Service and of the Faculty/College we again have a new Labour Government with a mandate to tackle seriously difficult national problems but with very limited resources to do so. Thus there are formidable problems to be solved before the demands of the NHS can be met. There is an insatiable appetite for Social Security funding. More than 32% (£100 billion) of the total annual government expenditure goes to Social Security; another 17% to Health and Social Services and 12% to Education. Tax payers do not want to pay more for Health and Social Services. Real growth areas are drug addiction, violent crime, obesity, "dumbing down". Fraud is so widespread that the Department of Health is advertising for a Fraud Supremo to accompany the Drug Czar.

The recent White Paper proposes a "third way" between the old bureaucratic command and control system and the fragmentation and distortions of the internal market. This will be led by primary care groups focused on population health. Anaesthetists could be further marginalised as these groups negotiate directly with Surgeons. One of the themes of the White Paper is the introduction by 2000 of "NHS DIRECT", a 24 hour nurse led telephone helpline. Wide access to interactive sources of information, be they helplines or World Wide Web, clearly empowers potential patients who will increase demands for detailed informed consent for anaesthesia.

The costs of giving an anaesthetic are not high but salary costs are considerably greater than drug costs. Consultant job plans presently have lots of blank spaces – room here for workload expansion? The wide availability of portable telephones and closed circuit television would make the introduction of the supervisory consultant fairly easy, e.g. the American system of one consultant supervising several, less trained, personnel in different operating rooms. Measurements of workload and complexity may form the basis of remuneration but increasing time spent on CME, CPD and simulators may leave nothing left for actual hands-on clinical work.

What of possible new clinical developments? Powerful new analgesics without respiratory side effects would transform the specialty but may create post operative problems in masking surgical complications. Opportunities here for Anaesthetists as peri-operative physicians? Elective transplant surgery will rapidly expand because of advances in transgenic animals and cloning of human organs and tissues. But if a viral stowaway in a Xenotransplant spreads from a recipient to others it could cause pandemics similar to Ebola, Marburg or even HIV (*Nature* 1998. 391. 320-324). Increasing drug addiction and dependence amongst anaesthetists seems likely in the future. Strategies described by Professor Milde in this issue must be developed now to contain this problem. Major advances in the specialty itself seem unlikely, particularly with the departure of intensive care and chronic pain work. At the start of a new millenium, and unlike the 1940's, anaesthesia has the feel of a specialty with a high degree of clinical expertise and safety but it seems to be in an evolutionary cul-de-sac, a constant target for cost cutting and a takeover by other groups. Sustained efforts must be made to ensure that there is a Royal College of Anaesthetists in 50 years time.

J Gareth Jones, Editor.

From the Registrar

I am delighted to be going into print for the first time in post as the College Registrar. I expect that this column will appear regularly in the College's Newsletter and that I will be able to take the opportunity to comment on various events which occur between publications, and in general about the College.

I hope that the design of the Newsletter in our Jubilee Year will bring it to the attention of Fellows, Members and registered trainees, and that they will want to read it and indeed get some enjoyment from it! The College is greatly indebted to ZENECA who continue to fund, with great generosity, the printing of our Newsletter. They have been marvellous benefactors over the years, and continue to be so. GlaxoWellcome have kindly joined forces with us. They are responsible for funding our new colour cover as a celebration of our Jubilee year and they have agreed to give us this continued support. We are grateful to them.

I joined the College in September and part of my remit is to try and improve communication externally. This must include not only Fellows, Members and trainees but also the rest of the medical profession, the NHS, the general public, the press and Government. It is an enormous challenge and I hope that Fellows, Members and trainees have noticed improved communications recently and feel that we are becoming more open, more ready to communicate, and very willing to explain as well as listen. The President and Council certainly wish an open and accessible College for Fellows and Members.

I seem to be the person to whom people come, be they anaesthetists or members of the public and press, to dispel or confirm myths widely held. Perhaps I can repeat a few. The first has received widespread publicity in the free medical press. We are told that there are an unusually high number of Fellows who are not paying their subscription. Let me dispel that myth. There are not. There is a small core of people who do not pay, but on the whole Fellows do pay their subscription and recognise its importance. There is one very good reason to pay. It is the College's responsibility to set and maintain standards. We are independent of Government and so we should be. If we are not funded by our own Fellows, then we will lose that independence, something I think most doctors would find more abhorrent than paying a subscription.

What about also dispelling a myth for trainees? After the recent exams held at the College, I am told that one of the common myths is that we have a quota of passes at the Final examination. This is not, and has never been, the case. How do we best allow exam candidates to know this, and in a way that we will be believed? I expect the increasing popularity of observer status at the exams will result in those observers returning to their departments to say what really does go on.

For one reason or another none of the Colleges appear to be wallowing in popularity at the moment. There is no doubt that as a College we do need to be proactive, we need to have an agenda, we need to have targets which we are trying to achieve, and we need to let our Fellows, Members and registered trainees know what these are.

I am currently planning a series of roadshows across the country so that the President, Chief Executive and myself can provide a forum for information exchange and discussion of College policy and local issues. We hope to have our first visit around April and will be asking for invitations to visit centres across the UK later in the year. I hope that we will be welcome and that the meetings can be used in a constructive way to bring us all together for the good of our specialty and for our patients. I would be interested to know who might consider inviting us?

Thanks to the contribution of many Fellows we have improved the immediacy and the appropriateness of our Newsletter. We have also created a College website and are excited by the potential for the spread of information in this way. The RCA website went live on 2 Janaury 1998. We have started off with information about the examinations, the College and its history. We will be expanding soon, Dr Peter Simpson from Bristol and member of Council, has been appointed as Editor. Patience is needed in this area. You all must appreciate the importance of accuracy of any documents put on the website. You can access the new Royal College of Anaesthetists website by using the address: **http://www.rcoa.ac.uk.**

There is no doubt that a correspondence column can enliven and enlighten any publication. The Newsletter is no exception. I hope that you will be provoked into writing, not only about what you see in this publication but also your comments on general issues relevant to anaesthetists which appear in other magazines which drop onto our doorsteps. This is a Newsletter for all Fellows, Members and registered trainees. We need you to contribute as much as you need us to communicate.

Juliet M Davies, Registrar.

The Evolution of the Faculty of Anaesthetists of the Royal College of Surgeons

by Professor T Cecil Gray, Past Dean, Faculty of Anaesthetists.

Before reviewing the foundation of the Faculty of Anaesthetists, it is necessary to summarise the evolution of the specialty in this country from the earliest days. From the London Society of Anaesthetists developed the Section of Anaesthesia in the Royal Society of Medicine. The offspring of the Section was the Association of Anaesthetists of Great Britain and Ireland, which, in 1932 stimulated the Conjoint Board of the Royal Colleges of Physicians and Surgeons to institute the first Diploma in Anaesthesia in the world.

The two major wars were important stimuli to the advancing specialty. The Great War "to end all wars", resulted in the evolution of the Boyle's anaesthetic "machine" and the Magill endotracheal tube. The 2nd World War produced large numbers of young General Practitioners, who, in the Forces, gained considerable experience in anaesthesia, many of them picking up a Diploma in Anaesthesia on the way. Then came neuromuscular block demanding obligatory advanced training in physics, physiology and pharmacology and last, but by no means least, the National Health Service instituted in 1948 made it possible for that ex-service body of anaesthetists to obtain specialist employment.

Before the 1939 war in the hospitals of this country, anaesthetics for surgical sessions, by and large, were administered by general practitioners and lady doctors, some married to surgeons and others who also did "clinics": in out-patient departments and at night it was left to the house surgeons: only very occasionally for a desperate or private case, would a surgeon call out his best anaesthetist. The late Ivan Magill used to tell how, after qualification, his first house job was at the Stanley Hospital in Liverpool where he was told by the surgeons that he was to give the anaesthetics - although his only training had been the usual twenty anaesthetics administered during his student days and he doubted whether he had completed those. In the event, he was so good at it that he became their favourite anaesthetist. It must be difficult for today's anaesthetists to appreciate the situation in the pre-war specialty. Up to the 1939 war, theatre uniform was worn only by the surgeons: in the operating theatre, anaesthetists usually wore their ordinary clothes simply covered by a white coat or theatre gown and a cap with or sometimes without a mask. There were in each large centre a very few full-time anaesthetists. Most of the distinguished anaesthetists of that time who held office in the Royal Society's Section of Anaesthesia and in the Association of Anaesthetists and most of the examiners for the DA, were still involved in general practice, which was the only sure way to earn a decent living.

Came the war and in 1948, the NHS was introduced, those who had passed the DA obtained full-time posts, the younger and less experienced finding junior hospital posts in which to get further training.

Only three medical Royal Colleges existed at that time - those of Physicians, of Surgeons and of Obstetricians and Gynaecologists. Fortunately, the RCP and the RCS had Presidents who were wise and far seeing and were much concerned in the planning of the NHS. The President of the RCP, Sir Charles McMoran Wilson (later becoming Lord Moran) was Honorary Consultant to St Mary's Hospital, Paddington: he was a strong and crafty man who dealt firmly with the BMA's reluctance to allow the Royal Colleges a major voice in the planning of the NHS. The President of the RCS handled the BMA a little better remaining friendly with its Secretary, Dr Hill, who was something of a bete noir to Moran. Perhaps this was a small factor in determining the status of anaesthesia in the Service.

The President of the Royal College of Surgeons was Sir (later "Lord") Alfred Webb-Johnson, Dean of the Middlesex Hospital; he was referred to by all his friends as Webb-J. With other far-seeing members of his Council, he appreciated that surgery was advancing rapidly and would continue so to do and, if that advance were to continue, they realised that there would have to be advances in anaesthesia and in the status of that specialty.

Webb-J's anaesthetist at the Middlesex Hospital was Dr Bernard Richard Millar Johnson, the Honorary Treasurer of the Association of Anaesthetists (1947-50). They were close friends and shared a special interest in the Army - Webb-J had been Chairman of the Army Medical Board during the war and Bernard Johnson - Johnny to his friends - had served in India and, after the war, he became the Honorary Civilian Adviser to the Army. There is no doubt that the future of anaesthesia in the post-war world would have been a frequent subject for discussion by this surgeon and his anaesthetist, as indeed it was for most of us.

Bernard Johnson was clever, dedicated and ambitious. He demanded from himself and his trainees the highest standards in both work and behaviour and, incidentally - amazing as it may seem today - he was one of the few anaesthetists who insisted on doing ward rounds to see his patients the day before their operation. Johnson longed and would do his best to see changes in the standing of anaesthesia and its practitioners.

As early as 1946, the Royal College of Surgeons had decided to build a Residence for Fellows onto the College with accommodation for department in the basic sciences: endowed by Lord Nuffield, it was built and became the Nuffield College. Web-J was keen to introduce into the College clinical disciplines allied to surgery and saw that a way of doing this would be to have "Faculties". Faculties would not only raise the status of their specialties, but would also increase the number of Fellows in the College, which, incidentally, would not be detrimental to its financial well being.

The concept of Faculties was readily accepted by the Council of the College and was very quickly implemented by the creation of a Faculty of Dental Surgery.

Of course, Webb-J would have told Bernard Johnson about this development and one can almost hear Johnson exclaiming "What about anaesthesia? What about a Faculty of Anaesthetists?" However, Webb-J's interest in having another Faculty in the College was such that it may well have been he who made the suggestion.

However that may be, it is most likely that it would be Johnson who suggested a meeting of Webb-J with the President of the Association of Anaesthetists, Dr Archie Marston, senior anaesthetist at St Mary's Hospital. They probably already knew each other through the RSM or other societies. They met and subsequently Webb-J proposed to the Council of his College that Marston should be co-opted to the Council. Such co-option of an outsider, I think, was then without precedent. That Marston's co-option was readily accepted was evidence of the commanding influence of the President, for, in those days, it is likely that there would be quite a few Council members who would look askance at a suggestion to co-opt an anaesthetist. However, some would be enthusiastic and principal among them would be Sir Henry Souttar of the London Hospital, who, incidentally, had taken over from Webb-J the Chairmanship of the Army Medical Council. Souttar was to become an ardent supporter of the Faculty and did everything he could to encourage it in the Council of the College.

Marston invited Webb-J to address the Council of the Association which he did, on 11 April 1947. He showed considerable enthusiasm for up-grading the specialty, but he was seriously concerned as to the academic standard of the Diploma in Anaesthetics (DA) as compared with a Fellowship in a Royal College. He pointed out that there was little chance of anaesthetists achieving consultant status in the NHS unless their qualification could be seen to be comparable to the two-part Fellowship examination in surgery and he stressed that this equality could only be achieved if anaesthetists *"were to continue their wartime interests outside the operating theatre in peace-time, in such areas as pre- and post-operative care, resuscitation, blood transfusion and oxygen therapy"*.* The DA was obviously inadequate, but, he suggested, if a Primary Examination in the basic sciences were introduced, it would upgrade the examination and successful candidates in both parts would be eligible for a Fellowship as would those senior anaesthetists who would be recognised for their contribution to the specialty. Time was short and this would be the quickest way to prepare for a Faculty.

The Association accepted these suggestions: the Conjoint Board of the RCP and RCS which was responsible for the DA examination were consulted and agreed to the proposed alteration in the regulations.

At the AGM of the Association of Anaesthetists held on 30 October 1948, the new regulations were accepted and the first two-part DA examination was held in November 1948. Upgrading of the examination was agreed on a vote, but there were members of Council of the Association who were sceptical about a Faculty seeing it as a threat to both the Association's educational activities and their control of the standard of the examination. However, negotiations with the Royal College were continued and it was obviously advisable to consult the Fellows (there was such a grade in those days) and Members of the Association. A Special General Meeting in London was called for 6 February 1948.

At that meeting the new President of the Association, Dr John Gilles of Edinburgh took the Chair.

---

* The italics are mine: for these words and details of Webb-J's address, I am grateful to Dr T B Boulton who allowed me to peruse pages from his forthcoming "History of the Association of Great Britain and Ireland". It saved many trips to London!

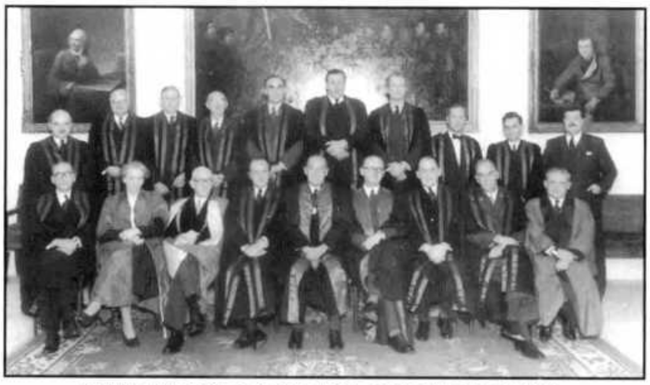
I was present and remember that meeting vividly - so very much was at stake. I strongly favoured a Faculty and as the discussion proceeded I became more and more apprehensive.

Marston, the past President, was the first speaker and put the proposition firmly: these are not his words but they indicate the spirit of his speech as I remember it. He warned of a dire future for the specialty if there were failure to take what would certainly be a very great step forward. Failure to grasp this opportunity would result in anaesthetists being second class citizens in the new NHS and ineligible for the position of consultant. He announced the establishment of the two-part DA examination, but stressed that even such a diploma alone would not provide the prestige of a Fellowship in a Royal College and recruitment to the specialty was likely to be very difficult.

The Founder of the Association, Dr Featherstone of Birmingham, Dr Langton Hewer, the Editor of the Associations' Journal and Dr Mennell, the Honorary Treasurer of the Association, expressed fears that the Association would be downgraded and would lose out, no longer having any control over the examination, its standard and the nomination of examiners. This was an understandable reaction from those who had been around when the Association was founded, but there was no doubt in the minds of the ex-servicemen present. They had become accustomed to having equality of rank and remuneration with their surgical and medical colleagues and were not inclined to see that change. Eventually, all was well. The greatly esteemed Dr George Edwards, Senior Anaesthetist of St George's Hospital, who had been Brigadier in charge of anaesthesia with the first army in North Africa, moved the motion "That this meeting is in favour of the proposal that the Association of Anaesthetists should apply for the formation of a Faculty of Anaesthesia within the Royal College of Surgeons of England". It was seconded by Bernard Johnson, also ex-service, with a full spirited, indeed very slightly aggressive speech and the motion was passed nem con. The result of this meeting was that the College quickly established the Faculty of Anaesthetists.

Who chose the members of the Foundation Board of the Faculty (figure 1), I have forgotten, but I can suggest with considerable confidence that it would be Marston and Johnson who made the decisions, almost certainly assisted by the President of the Association, Dr John Gilles. I was genuinely shocked when, one evening shortly after that crucial meeting, I was rung up by Bernard Johnson asking if I would serve on the Board of Faculty. I suspect that my friend, Dr Vernon Hall, the only other surviving Foundation Fellow, may have been equally surprised, although his nomination was certainly more to be expected than mine. There was no hesitation in my reply. In the event, Professor Edgar Pask, Dr Ronald Woolmer and I were to represent the "Members" of the Faculty who would be those who were not elected to the Fellowship but who were practising full-time anaesthesia with a one-part DA.

The first meeting of the Board of Faculty was held in the Library of the Royal College of Surgeons. One of its first tasks was to elect a Dean and Vice-Dean: not surprisingly Archie Marston was elected Dean and Bernard Johnson Vice-Dean. The next important task was to elect foundation Fellows.



THE FIRST BOARD OF FACULTY

Back Row (from left to right): Dr T C Gray, Dr F T Evans, Dr V F Hall, Dr B L S Murtagh, Dr A H Musgrove, Dr W A Low, Dr R F Woolmer, Dr G S W Organe, Professor F A Pask, Mr W F Davis *(Secretary)*

Front Row (from left to right): Dr J H T Challis, Dr K G Lloyd-Williams, Dr E S Rowbotham, Dr B Johnson *(Vice-Dean)*, Mr A D Marston *(Dean)*, Dr I W Magill, Dr G Edwards, Dr C Langton Hewer, Dr R E Pleasance

Obviously, the nominated Board had to agree to elect themselves and they included the three who represented the members. The election of foundation Fellows of the Faculty took several meetings and I remember the Dean observing that, in choosing foundation Fellows, we had to be generous so as to ensure that with the two-part diploma should be given a Fellowship and also those with the one-part diploma who had distinguished themselves in anaesthesia or had given long and recognisably valuable service to the specialty. A few senior anaesthetists, without a DA, but with a good local reputation, were also accepted for the Fellowship.

Thus was the Faculty of Anaesthetists launched and its Fellows can look back with some pride on its achievements over the nearly fifty years. They have justified the optimism of its founders and the remarkable success of the Faculty's Fellowship transformed a Cinderella specialty into one in the front line by ensuring that its Fellows had the skill, experience and knowledge to advance anaesthesia and the enterprise to form branch sub-specialties of Paediatric and Obstetrical Anaesthesia and also, one badly needed, Pain Management.

The climactic final achievement has been the rise of an independent Royal College of Anaesthetists without rancour in the parent College. The debt that this new Royal College owes to the Faculty and its inspirational founders, Lord Alfred Webb-Johnson and Dr Archibald Marston, should never be forgotten.

It has been a great pleasure to recall and pay tribute to those who launched such a remarkable and successful ship.

A Physicist in Anaesthesia

by Professor W W Mapleson, Professor Emeritus of the Physics of Anaesthesia, University of Wales College of Medicine, Cardiff.

I became involved in anaesthetics when I was nearing the end of my PhD, on "Point Discharge in Atmospheric Electricity", in 1952 in Durham. I saw an advert which read "Wanted in the Anaesthetics Department in Cardiff, someone with a wide knowledge of physics, physiology or pharmacology". I decided that this would give me some useful interviewing experience. To my acute embarrassment I was offered the job and I was faced with making a decision. So I said to the Head of the Department, Dr Mushin as he then was, that I would like a day or two to think it over. I think he was a bit taken aback by this because it wasn't the sort of thing anyone said to Mushin. I decided to accept, on the basis that "it would do for five years". In fact the relationship with anaesthesia has so far lasted for forty-five years.

When I joined the Department, in October 1952, it was in the Cardiff Royal Infirmary. The staff consisted of William W. Mushin; his secretary, Muriel Fairweather; a technician, Ken Hillard; and a records secretary. In addition, all the clinical anaesthetists were regarded as members of the Department. Mine was the first non-medical academic appointment in the Welsh National School of Medicine (now the College of Medicine) in Cardiff, and it is a tribute to Professor Mushin that he foresaw the contribution which basic scientists can make to the development of medicine. This is now widely accepted, but 50 years ago it was revolutionary.

The department then had a well-equipped mechanical workshop and a laboratory which contained benches and cupboards but little equipment beyond some glassware and a bunsen burner. My first assignment was to make measurements of the muscle relaxation produced by gallamine triethiodide (Flaxedil) which was the first synthetic muscle relaxant. For this project, Professor Mushin had obtained a grant of £250 from the Association of Anaesthetists to buy a nerve stimulator; but I convinced him that, with "that amount of money", I could equip the department for electronics and build our own stimulator. Mushin specified that we should stimulate the ulnar nerve at the wrist and record the force of the contraction of the short muscles of the thumb. Ken Hillard constructed the force-measuring equipment and I constructed the stimulator. Both were state of the art: the recording system used a hot wire moving over heat-sensitive paper instead of the then-standard smoked drum; the stimulator incorporated pulse techniques which I had learnt during my two years of National Service in the RAF.

We decided that the measurements should be made in conscious volunteers to avoid the extraneous movements that would be inevitable in theatre. While supramaximal stimuli are considered essential to ensure return to baseline when the relaxant has worn off, I felt that, to obtain an adequate supply of volunteers (all members of the Department) we would have to use submaximal stimuli. I thought that stability of contraction would be achieved by controlling, not the voltage applied to the stimulating electrode, but the current through it. This proved inadequate but the problem was eventually solved with the "multi-wick electrode". This comprised five narrow electrodes, ranged side by side, with an equal controlled current through each. The aim was to produce a uniform current density across the wrist, so that relative movement of nerve and electrode would not alter the number of nerve fibres stimulated. And it worked! To quote the published paper: the contraction strength at the end of an experiment "rarely deviated by more than 5%" from baseline. The eventual publication was also innovative in that it included some pharmacokinetic modelling of the results, laboriously worked out on an electro-mechanical calculator. The volume of Anaesthesia in which the publication appeared, in 1955, contained an advertisement for Flaxedil, but it also had one for "Macfarlan's Anaesthetic Ether" and, not unconnected with the latter, one for the Baldwin "Statigun" to detect static charges. Happily, explosions are no longer "the constant worry of the anaesthetist"!

While I was waiting for suitable volunteers I began a little pot-boiler on breathing systems. Professor Mushin had drawn out five semi-closed systems and said "Have a look at these and see if you can work out what is required to eliminate rebreathing. There is a chap called Molyneux in Newcastle who has analysed the first one, but I'm not sure if he has got it right and no one has looked at the others". Mushin told me nothing about the systems, but I needed some means of referring to them so I just labelled them A, B, C, D and E. I was astonished to find that, within two or three years of publication (in 1954 - before the gallamine paper) they were being referred to as the "Mapleson A", "Mapleson B" and so on. Thus are reputations made! It was generous of Mushin to allow me to publish the paper just in my own name. However, I would like to take this opportunity of apologising to Dr Jackson Rees and, posthumously, to Sir Ivan Magill for not acknowledging them as the creators of systems "D" (strictly, the later "F") and "A" respectively.

My main research interest over the years has been the uptake and distribution of anaesthetics. My first mathematical model of the uptake and distribution of an inhaled anaesthetic took the form of a network of capacitors and resistors - a "passive" electric analogue computer. Having had the idea, I discovered that the technique had been used in other fields - where physicists had worked with clinicians - but Cardiff was the first Department to apply it to anaesthesia. I demonstrated the analogue at a meeting of the Anaesthetic Research Society (then the Anaesthetic Research Group) in 1960, showed a film of it at a biophysics congress in Stockholm in 1961, and even took the computer, assembled in a purpose-built attaché case (constructed by Ken Hillard), to New York for the conference on the "Uptake and Distribution of Anaesthetic Agents". There I was able to use the computer to make additional calculations between the first and second days of the conference - shades of the modern laptop computer!

That conference was a nice demonstration of the fact that there is a right time for an invention: two other electric analogues of uptake and distribution were reported, and Ted Eger presented the first digital computer model. While waiting for a digital computer service to become available in Cardiff, we made good use of the electric analogue. In 1963 we programmed it for the newly available methoxyflurane to predict how that very-high-solubility agent might behave clinically. We demonstrated it at the Anaesthetic Research Society meeting in Cardiff that year and I remember Alex Forester, then head of the Anaesthetics Department in Glasgow, cautiously giving his first methoxyflurane anaesthetic to the analogue - a forerunner of present-day patient simulators.

Since then, other computer-program models have been written in the Department: in Fortran (by Peter Allott), in BBC Basic, and in the form of a spreadsheet (by Valerie Flook, one of my first two research assistants, who is currently using it to calculate safe decompression procedures in deep-sea diving). The most interesting version was written in the 1980s by Norman Davis as part of his PhD project. This was a detailed physiological model for injected agents which we considered required the separate representation of all forms of the drug: ionised and unionised dissolved in water, dissolved in lipid, and bound to protein.

A logical development of a computer model of pharmacokinetics is to use it to control the administration of an anaesthetic or, to put it more tactfully, to assist the anaesthetist in the control of anaesthesia. Our first attempt in the early 1970s was before the days of on-line computers, so the running calculations for control were done by four physicists, (Peter Allott, Bob Chilcoat, Brian Willis and myself) each with an electronic calculator one of which actually had four memories and a square-root key! Alan Steward, a physiologist cum pharmacologist, was responsible for the overall running of the project.

A subject which is inextricably linked with uptake and distribution is the use of low fresh-gas flows in inhalational anaesthesia. In fact it was the need to tackle this problem, when that "new, expensive anaesthetic" halothane was introduced in 1957, that stimulated my interest in uptake and distribution. Subsequently, each time another "expensive" anaesthetic was introduced, I was asked to talk about its use with low flow, either just to the Department, or at the Warsaw European Congress in 1990, or at the Edinburgh ALFA symposium in 1996. This last was the first to address the problem of how to control the fresh-gas flow and concentration in the first few minutes of anaesthesia instead of the much simpler problem of how to do so once a steady state has been achieved. It has recently appeared in anaesthesia.

An enduring interest of Professor Mushin's which I shared was lung ventilators. Together with Leslie Rendell-Baker and Peter Thompson, this culminated in the book "Automatic Ventilation of the Lungs", which ran to three editions and which John Lunn irreverently dubbed "The Puffing Bible". My contribution was in analysing the relationship between the mechanical construction and the resulting waveforms of flow and pressure produced in the patient's respiratory system. Curiously, there is little agreement on the "best" waveform. The subject is bedevilled by the many mathematical connections between the different variables. Our approach (that is, John Lunn, Bob Chilcoat and myself) was to vary frequency, tidal volume and inspired oxygen concentration in such a way as to maintain constant levels of mean airway pressure and of arterial tensions of CO2 and oxygen. We showed that wide changes of frequency then had no important effect on physiological dead space, cardiac output or venous admixture. On the other hand, recent work by John Mecklenburgh for his PhD, which I supervised, suggests that when the ventilator is merely assisting the breathing of a conscious subject, waveform of flow or pressure may indeed be important, and even that different subjects may prefer different waveforms.

My 45 years in the Department have now spanned three Heads of Department. With Professor Mushin, since he appointed me in the first place as a raw not-quite-PhD researcher, it was inevitable that our relationship would always remain in some degree, and in the nicest possible way, that of the iminence grise and the young newcomer. Thus he played a major part in determining what projects I worked on, although he then allowed me free rein in how I pursued them - with the regular discussions that need to go on for any research project to be successful. When Professor Michael Vickers arrived, I was already something of an authority on some subjects, and I had my personal chair. Therefore our relationship was nearer to that of Mike being "first among equals". So I had a freer rein. Apart from supervising, or co-supervising, a series of PhD theses (those of Bob Chilcoat, Norman Davis, Couto da Silva, John Mecklenburgh and Takashi Asai) I found myself becoming involved in any mathematical or statistical aspects of clinical projects in the Department - but always, as with Bill Mushin, with frequent discussions with Mike Vickers of planning and progress. My work was evidently appreciated by Mike because, when I retired in 1991, he arranged for me to have a formal half-day-a-week consultancy for the benefit of young researchers in the Department. This has continued very amicably under our new head of department, Professor Michael Harmer, and has provided me with a steady stream of new problems to be solved. Together with writing up projects that were incomplete at the time of retirement, and requests for help from various Departments outside Cardiff, I find myself still working a 40-hour week. The main difference is that most of the time I now work at home, with a pleasant view of the hills behind Cardiff, instead of looking out on the blank concrete wall of the operating-theatre block.

My first association with the College, then the Faculty, was in 1963 when I was asked to lecture on "The Uptake and Elimination of Inhalational Anaesthetics" on the "Course on Anaesthetics". I continued to lecture on that subject on every such course until January 1996, and for many of those years I also lectured on Anaesthetic Breathing Systems. Mushin always insisted that no pains should be spared to make every publication and every lecture as clear and as simply expressed as possible, and the main tool for achieving this in the uptake lectures has been the water analogue. My notes for that first lecture include a primitive form of the analogue which I suspect I devised expressly for the occasion. Over the years I have progressively developed the analogue, eventually finding a satisfactory means of incorporating the concentration and second-gas effects in 1987. For the breathing-system lectures, the main tool was animated overhead projection, a technique I developed after seeing Peter Armitage the statistician use it in a lecture at the RSM.

The College honoured me with the Faculty Medal in 1981, the Dudley Buxton medal in 1992 and, what I prize most, Honorary Fellowship in June 1996. I hope that I shall continue to cerebrate adequately to contribute to anaesthesia for a few more years yet.

This is an edited version of a similar article published in "Essays on the First 50 Years 1947-97" Edited Appadurai IR and Horton JN Department of Anaesthetics, University of Wales College of Medicine, Cardiff. Blackwells 1997.

Royal College of Anaesthetists Newsletter March 1998, Issue No. 39

Drug Dependence Among Anaesthetists in the United States

by Professor L N Milde, Chairman, Department of Anaesthesiology
Mayo Clinic, Arizona, USA.

Introduction

In a society where increasing numbers of people are becoming dependent on drugs it is not surprising that a minority of doctors cannot avoid the self-use of drugs with which they treat their patients. Although the first self-use of drugs may be difficult to explain, subsequent chemical dependence (drug addiction) is recognised in the United States as a chronic progressive disease which is characterised by compulsion, the loss of control over drug use, and continued use despite adverse consequences. It is associated with stress, a lack of a constructive outlet for stress, a willingness to experiment with the self use of drugs, and a belief that physicians are invulnerable and can control their own drug use. The easy access to potent drugs by anaesthetists is a contributory factor. Abuse of drugs by physicians is more common than dependence. Some abuse drugs "recreationally" to feel better, others self-medicate to relieve illness or stress. The use of alcohol typically takes years to become dependent while dependence to sufentanil occurs almost after the first use.[1]

Policy For Managing Chemical Dependence

Chemical dependence is the most common occupational hazard within the speciality of anaesthesia in the USA.[2345] In 1986 the American Society of Anaesthesiology (ASA) produced a statement that "it is important that anaesthesia departments have mechanisms in place before a problem develops so that when realistic concerns or reasonable evidence for drug or alcohol abuse surface, appropriate, rapid, and safe action can be taken". The (ASA) produced a paper entitled *Chemical Dependence Guidelines of Departments of Anaesthesiology.*[6] It offers both a plan for education about chemical dependence and a plan for action including a sample chemical dependence policy. This states that:

1. Chemical dependence is a disease.
2. Untreated or relapsing chemical dependence is incompatible with the safe clinical performance in anaesthesia.
3. It is the duty of all members of the department to share their concerns about chemical dependence ... with a designated resource person.
4. Any member of the department suffering from active chemical dependence shall immediately be placed on leave of absence.
5. Return from medical leave for chemical dependence shall be governed by the departmental re-entry policy.

The Chemical Dependence re-entry Policy of the ASA states that:

1. Leave for treatment of dependence shall be recorded in the member's personnel file and shall be released only upon the written permission of that member.
2. If the Head of Anaesthesia, in consultation with a specialist in chemical dependence, determines that the performance of anaesthesia by a member is impaired due to chemical dependence, then the member must resign from the department.
3. If as in (2) it is determined that the performance of anaesthesia is compatible with recovery from chemical dependence, the member shall sign a re-entry contract before being granted staff privileges.

The ASA guidelines for a re-entry contract include:

1. An actual contract should be drafted by legal counsel.
2. The treating physician must be qualified to treat chemical dependence.
3. The recommendations of the treating physician must be followed including aftercare programs and continued abstinence from substances of abuse.
4. The member must agree to random blood/urine tests screening for drugs
5. All medical supervision and drug screening must be done by a physician outside the department of anaesthesia.
6. Violation of this contract (evidence of drug abuse or positive drug screen) results in termination of staff privileges. The department has the option to reinstate staff privileges after further treatment.

In 1991 the ASA reported that the incidence of chemical dependence among anaesthesiologists was 0.7 % / year. Most were residents (87%), male (88%), and most of these were in their first two years of anaesthesia training. Of those that were faculty members (11%) most were young in entry level positions (instructor, assistant professor). A family history of chemical dependence occurred in 32%. Twelve percent joined anaesthesia training programs with a prior history of documented substance abuse. A large percentage were high achievers; most have been in the top or middle third of their medical school class.

Narcotics are the most common substances of abuse among anaesthesiologists with fentanyl being the most common (57%) and sufentanil being next (8%). In this study 48% successfully returned to work but the relapse rate of those returning to work was 21%. There were 12 deaths reported from narcotic use. The overall success rate of a California program[7] was 66% among anaesthesiologists. Of the recovering anaesthesiologists 96% continue to practice in their speciality. This indicates that intensive inpatient treatment and supportive aftercare play an important role in the success of recovery and contradicts the pessimism expressed in an earlier study in which the relapse rate among anaesthesiologists was reported to be 66%.[8] In that study the first sign of relapse was death in 16%. The same relapse rate occurred despite the length of aftercare (as long as 8 years).

Symptoms Of Chemical Dependence

The symptoms typically found in those personnel chemically dependent on narcotics are:

1. Unusual changes in behaviour, with frequent mood swings; periods of depression, anger, irritability, alternating with periods of euphoria
2. Withdrawal from family, friends, and colleagues
3. Obtaining ever increasing quantities of narcotics for their patients
4. Obtaining inappropriately high doses of narcotics
5. Sloppy and unreadable charting
6. Preference for working alone (to use anaesthetic techniques without narcotics, falsify records, and divert narcotics to personal use)
7. Refusal of lunch or coffee breaks
8. Frequently volunteering to relieve others
9. Volunteering for extra cases (especially cardiac cases where large amounts of narcotics can be used)
10. Volunteering for extra on-call
11. Frequenting the hospital when off duty (to stay near the drug supply)
12. Frequent requests for toilet relief (to use the drugs)
13. Disappearing between cases for long periods
14. Complaint of excessive pain by patients out of proportion to the amount of narcotic charted on the anaesthesia record
15. Wearing long sleeved gowns (to combat the subjective feeling of cold they experience when using narcotics)
16. Pinpoint pupils
17. Displaying evidence of withdrawal, diaphoresis and tremors
18. Weight loss and pale skin
19. Witnessed self administration
20. Coma or death

The primary trait of the disease is denial, the refusal to accept the reality of the chemical dependence. Those dependent on drugs are lonely isolated individuals unable to reach out for help. They feel guilt at their inability to stop using the drugs, shame at the prospect of being discovered, fear that, if detected, they will lose their medical licenses, career, and family. Most want to be detected because they cannot reach out for help. Family members are often aware of the addiction but they too feel guilt, shame, and isolation and therefore participate in a conspiracy of silence. They ignore obvious symptoms, make excuses to themselves and others for the addict's behaviour, and avoid taking action on suspicions. Many times the family members do not know to whom to go for advice and help. This is why education not only for the anaesthesia personnel but also for their family members is vitally important.

Management of Individuals with Chemical Dependence

Once a person is suspected of chemical dependence an intervention is planned. This is a structured meeting in which the addict is confronted with the evidence and consequences of the disease. The purpose is to initiate a program of recovery. Carefully planned in advance, the meeting is led by an experienced person, and may be attended by family members and colleagues. An intervention is not a punitive attack but a *supportive* act of caring. It should stress concern for the well being of the individual, his/her family and patients. At the time of the intervention a definitive plan for inpatient treatment of chemical dependence must be in place. At our hospital the addict is personally escorted to a psychiatrist specialising in chemical dependence for immediate evaluation. Failure to comply with this action results in immediate dismissal. It is the psychiatrist who determines whether or not the person is chemically dependent. Although denial is common during the intervention, most admit to addiction either on the way to the psychiatrist or at the psychiatrist's evaluation. If deemed dependent the person is immediately admitted to an in-patient facility for the treatment of chemical dependence so that no time is allowed for the addict be alone.

A one to two month period of inpatient treatment is followed by a variable length intensive treatment in an outpatient program (0-6 months). The purpose is the safe withdrawal of the addictive drugs, help in accepting chemical dependence as a chronic disease to be treated the rest of life, and the development of different attitudes and coping skills that will help maintain a drug free lifestyle (detoxification, education to overcome denial, and behaviour modification therapy). This is followed by years (if not a lifetime) of an aftercare program including group sessions, counselling, random drug screens, and the administration of alcohol or narcotic antagonists, if necessary.

Criteria For Return To Work

Whether or not an anaesthesiologist who has been addicted to narcotics should be allowed to return to the workplace is the subject of debate. While there is no documented evidence that anaesthesia personnel addicted to narcotics have harmed any patient, there is strong evidence that an addicted person is a safety hazard to himself (coma or death from overdose or suicide). The criteria for a successful return to work include:

1. Completion of a treatment program for both the addict and close family members
2. Acceptance of the disease of addiction and motivation to remain drug free, with acceptance of the need for continued treatment and monitoring
3. Support within the Department of Anaesthesia, the family, and colleagues for the continuing aftercare of the addict.

A continuing care contract is essential for successful recovery to continue. This contract may be with the treatment centre, the anaesthesia department, and/or the State Medical Society. The contract at our institution is very strict and the recovering addict agrees to:

1. Abstain from all mood altering drugs for life
2. Attend weekly self-help group meetings
3. Attend weekly group meetings for recovering physicians
4. Attend a weekly aftercare therapy session with a counsellor specialising in chemical dependence
5. Meet monthly with a primary care physician who is responsible for ongoing medical care
6. Meet monthly with a psychiatrist specialising in addition
7. Submit to random, witnessed urine drug screening
8. If narcotics were the addictive drugs, take naltrexone 3x/week before a witness (this provides extra physical insurance against relapse and reassurance to the department that an anaesthetist impaired by the use of narcotics will not be caring for patients)
9. If alcohol was the additive drugs, take disulfuram daily before a witness
10. Meet monthly with the Department Chairman (faculty) or Residency Program Director (residents)
11. Report monthly to a member of the State Society's Impaired Physicians Program Participants in the recovering addict's aftercare treatment program must give formal written evaluation to the State's Medical Society every three months.
12. Participate in family therapy
13. Within the workplace the recovering addict cannot be on call for three months or handle narcotics for three months following the return to work.

While these criteria are strict, they offer significant structure to the aftercare program and are necessary for a successful recovery. If the recovering addict does not comply with these criteria they are dismissed from the department. To date, all chemically dependent members of our department who have successfully completed an in-patient program and remain in a highly structured aftercare program have had no relapse over the six years since the start of our program.

Prevention is the key

Ways to prevent addiction include strict accountability of drugs and education. At our hospital, all narcotics and sedatives (benzodiazipines and ketamine) are locked in an automated drug dispensing unit (PYXIS®). Only a limited number of people have access to it. Access requires entry of a personal identification number and entry of a specific patient name. Each type of drug is kept in a separate drawer that opens only when that drug is requested. Visual count of the number of drug vials left in the drawer of the unit must be confirmed to the unit before the drawer is closed. If there is a discrepancy between the unit's count and the visual count, the person whose identification number was entered for the previous item is asked to explain the discrepancy. Unopened vials not used during the surgery are returned. Drugs drawn into syringes, but not used, are wasted with a witness present. The system limits easy access to drugs but certainly doesn't prevent drug abuse.

There must be education of medical students, residents, consultants and their family members concerning the prevalence as well as the signs and symptoms of the disease. Opportunities for reduction of stress should include discussion of job and emotional stresses and/or via exercise. Education has proven the most useful because family members and colleagues have known to whom they can go to discuss their concerns. The earlier that treatment is started following chemical dependence, the better the chances of lifelong recovery.

REFERENCES

[1] ***Arnold WP: Environmental Safety Including Chemical Dependency in Miller RD: Anesthesia 4th Edition, New York: Churchill-Livingstone 1994, pp. 2681-2696***

[2] ***Gallegros KV et al: Addiction in Anesthesiologists: Drugs access and Patterns of Abuse. QRB 14 (1988) 116-122***

[3] ***Lecky JH et al: A Departmental Policy Addressing Chemical Substance Abuse. Anesthesiology 65 (1986) 414-417***

[4] ***Ward CF, Ward GC, Saidman LJ: Drug Abuse in Anesthesia Training Programs JAMA 250 (1983) 922-925***

[5] ***Talbott G, Gallegros KV, Wilson PO et al: The Medical Association of Georgia's Impaired Physicians Program JAMA 257 (1987) 2927-2930***

[6] ***American Society of Anesthesiologists: Chemical Dependence Guidelines of Departments of Anesthesiology, 1991***

[7] ***Pelton C, Ikeda RM: The California Physicians Diversion Program's Experience with Recovering Anesthesiologists CSA Bulletin 1992 22-30***

[8] ***Menk EJ, Baumgarten RK, Kingsley CP et al: Success of reentry into anesthesiology training programs by residents with a history of substance abuse. JAMA, 1990 263: 3060-3062.***

What is the Future of CME?

by Professor R M Jones, St Mary's Hospital Imperial College, London.

Medicine is a self-regulating profession. This is a privilege granted by the State through an act of parliament. The Medical Act of 1858 provided the basis for this self-regulation through the establishment of the General Medical Council. It is important to emphasize that professional independence is a privilege, not a right, and that the maintenance of independence cannot be assured without competent self-regulation[1].

In two articles published last year by Sir Donald Irvine, President of the GMC, the point is persuasively made that the performance of doctors needs constantly reviewing in a world that is rapidly changing[1,2]. This change encompasses both the recent enormous and ever increasing growth in medical knowledge as well as the increasing awareness and sophistication of the general public in health matters. I would commend both of these articles to all anaesthetists; the message they convey has profound implications for the way that all specialties, including Anaesthetics, self regulate their standards of practice and performance.

Participation in Continuing Medical Eeducation (CME) is an essential activity and is crucial to maintaining an appropriate knowledge base and in developing new skills. As a generalisation, the half-life of medical knowledge is of the order of 10 years. Thus, anaesthetists in their forties and fifties would needed to have renewed a very significant proportion of their knowledge base in order to be as well informed as a newly appointed consultant. The problem is with the sheer pace of change, not only in that aspect of medical knowledge needed to practice anaesthesia in the 1990's but also in the changing medico-legal environment in which we all practice and the impact on medicine of the information technology revolution.

The increasing importance of CME and CPD (Continuing Professional Development) is highlighted by the fact that during the UK's presidency of the European Union the CMO has chosen CME and CPD as the principal topics for a conference held during a meeting of EU Chief Medical Officers. This conference heralds an acceptance that there should be as much harmonisation of the CME requirements and activities of member states as possible. N.B. the terms CME and CPD are not synonymous; CPD implies activities that are not directly patient orientated, such as management, educational, budgetary and ethical issues. In addition, at the most recent meeting of DOCME (Directors of Continuing Medical Education) last October, this advisory body recommended to the Academy of Medical Royal Colleges that participation in CME and CPD should be mandatory not voluntary. This recommendation was made in the light of the growing pressure from patient groups, management, the GMC and defence organisations, that the profession be seen to be ensuring that all doctors are up to date and possess the core skills of their individual specialties. In effect DOCME recognised that unless the profession self-regulates this aspect of maintaining professional standards, the privilege of self-regulation will be lost.

Update - Information

EUROPEAN SPECIALIST MEDICAL QUALIFICATIONS AMENDMENT REGULATIONS 1997

On 31 December 1997, the above amendment came into force allowing greater flexibility in the transitional provisions which enable existing specialists to be entered onto the Specialist Register. In summary:

- The transitional period within which existing specialists may apply to the General Medical Council to have their names included on the Specialist Register is extended to **1 December 1998**.
- Greater flexibility has been introduced such that experience in a specialty and/or up to 12 months further training undertaken at the recommendation of the Authority, in addition to UK qualifications, are to be recognised by the STA in assessing a doctor for entry to the Specialist Register. Doctors who wish to be assessed for entry to the Specialist Register under these regulations need to apply to the STA, via the Royal College of Anaesthetists by **1 April 1998**.
- Doctors who need to undertake extra training (of up to 12 months) at the recommendation of the STA, can apply for entry to the Specialist Register before **1 December 1998**, but will be entitled to inclusion in the Specialist Register if they satisfactorily complete their further training by **1 December 2001**.

Further information on the arrangements for assessing doctors for entry to the Specialist Register under these Regulations will be issued shortly by the Specialist Training Authority.

Anaesthetists wishing to take advantage of these changes to transitional provisions are reminded of the deadlines and should address all correspondence to the College to **Mr Guy Wilkinson in the Professional Standards Directorate**.

EXAMINATIONS CALENDAR 1998/99

The Royal College of Anaesthetists Examinations Calendar for August 1998 to July 1999 has now been published and can be obtained from the Examinations Directorate at the College.

NEW PUBLICATIONS

Further to recent changes in the Regulations for the Primary and Final Examinations for the FRCA, an updated version of the Regulations may be obtained from the Examinations Directorate at the College (Direct Tel: 0171 813 1880). Sections that incorporate changes from the May 1997 version are listed inside the front cover for quick reference.

Update - Information

ANSWERS TO MOST FREQUENT QUERIES ABOUT THE EXAMINATIONS

As a quick reference, here are the answers to the questions we get asked most frequently about the FRCA examinations:

(1) Candidates need 12 months of approved training in the United Kingdom or Ireland before they can sit the Primary FRCA examination. No other overseas training is accepted.

(2) Candidates may not sit the Primary FRCA examination more than 4 times, and the Final FRCA examination not more than 6 times.

(3) Candidates need 30 months of anaesthetic training before they can sit the Final FRCA examination. Up to 12 months only of overseas anaesthetic training can be accepted; at least 18 months must be spent in approved posts in the UK or Ireland.

(4) The Primary and Final FFARCS(Ireland) examinations are considered entirely equivalent to the Primary and Final FRCA examinations respectively.

(5) Attempts at the FFARCS(Ireland) examinations are not currently included as attempts at the FRCA although this regulation will be reviewed in due course.

If you require any further information, please do not hesitate to contact the Examinations Directorate at the College.

USEFUL TELEPHONE NUMBERS

Royal College of Anaesthetists
Tel: 0171 813 1900
Fax: 0171 813 1876

Direct Tel:
Education (Courses & Meetings): 0171 813 1888
Examinations: 0171 813 1880

Direct Fax:
Finance (Subscriptions): 0171 580 6325
Training and Education: 0171 636 8280

	Extension
Database Administrator - *Ms D Huffer*	**112**
Examinations - *Ms A Mattis*	**126**
Individual Trainees - *Mrs G Wybrow*	**111**
Hospital Recognition - *Miss G Rowe*	**109**
Education - *Miss K Sayer*	**129**
Subscriptions - *Mr T South*	**105**

It therefore appears likely that participation in CME will become compulsory in the future. Indeed, it is already for Fellows of the Royal College of Gynaecologists who will publish a white list in January 1999 of members who have completed the necessary CME requirements. There was a general feeling, aired at a recent workshop on CME organised by the Standing Committee on Postgraduate Medical Education (SCOPME), that not only was compulsion a likely event but that the pressure on Colleges to produce "white lists" was going to be difficult to resist.

Thus, it seems very likely that participation in CME is going to become a compulsory and potentially increasing part of all our lives. I fully appreciate that many people reading this article will find this observation an irritation (at the very least) and I must emphasize that this is not something being thought up and imposed by the Royal College of Anaesthetists. It is the result of increasing external pressures from a variety of sources which all Colleges and Faculties are having to face. In accepting the inevitability of compulsory CME, two issues emerge and need addressing. First, who is going to fund compulsory CME/CPD and second, what form should CME/CPD take. Both issues are difficult.

Even the relatively simple CME requirements and associated activities that have currently evolved are thought to cost in the region of £2000-£3000 per person per year. Currently the average amount available per trust appears to be in the region of £400 with the largest sum available said to be £1200 per year. If CME is compulsory who is going to pay for it? What form should CME take and how should it be recorded? There seems little doubt that passive participation in CME, such as attending lectures and conferences, appears not to have much impact on clinically relevant outcome measures3. However, active involvement in workshops, round table discussions and the like probably is more effective and CME should develop with a greater emphasis on the active involvement of participants. The problem is that this type of active-participation CME is much more labour intensive, time consuming and costly.

There has been much debate on how best to record CME activity. There is no doubt that the current points system has many drawbacks but the problem is quite what to replace it with. As in most aspects of CME the RCA cannot and would not wish to act alone on this issue. DOCME exists in order to harmonise the CME requirements of all Colleges and Faculties. As the format of CME and CPD evolves and develops so too will the systems for recording these activities. Another potentially contentious issue is to what extent, if at all, there should be an assessment whether participation in CME activities has increased an individual's knowledge base. This is an activity that could eventually result in a form of recertification.

There is also a growing awareness that every anaesthetist, of whatever status and affiliation, practising in circumstances where they may be autonomous (ie. unsupervised) must participate in CME and that they should keep up to date in the core knowledge and skills of our specialty. It seems very likely that each specialty will be asked to provide an outline of the core skills and knowledge required for safe independent practice. I have been working with the Chairmen of the Education Committees of the College (Pierre Foex) and the Association (Rajinder Mirakhur) to start to define these "core topics" and to initiate a discussion of their scope. I would very much welcome any suggestions concerning what topics and skills should make up this core (should, for example, each of us be skilled at using the fibre-optic laryngoscope?). Society has the right to expect that any independently practising anaesthetist should have up to date core knowledge and skills; this expectation would include non-consultant career grade staff as well as GP clinical assistants. It will be for the College and other competent providers to ensure that workshops and courses covering the agreed core topics are available on a regular rolling basis and accessible to all. In this respect discussions are ongoing concerning the organisation of regional CME activities and the use of teleconferencing is also being explored.

CME is just one aspect of professional standards and increasingly departments will need to be accountable for the quality and standards of care that they provide as a whole. Ultimately, this collective responsibility lies with the clinical director but each individual in the department bears a share of this collective responsibility in addition to the purely personal responsibility of keeping abreast of developments, practical as well as theoretical. However, the CME needs of individuals vary greatly but what an individual perceives as what is needed may not be what their peers would think. Self evaluation programmes are becoming available to assist an individual in identifying their educational needs. Used in conjunction with a review of quality of practice at the local level, and more goal orientated CME activities, self evaluation programmes should find a useful place in ensuring optimal use is made of the time available for continuing education.

I conclude by emphasizing the fact that the manner in which CME is evolving is something that is being driven by a variety of outside sources including the defence organisations, the GMC and patient interest groups. In a real sense society is demanding that not only do doctors keep up to date but that this is a recorded and verifiable phenomenon. Since becoming Director of Continuing Education and Professional Development I have received a number of letters complaining of the increasing regulations imposed on our professional lives and asking if participation in CME has ever been shown to do any good (there was yet another letter along these lines in the January Newsletter). Through the Professional Standards and Continuing Education and Professional Development (CEPD) Committees, the College has a duty to ensure that these external pressures are responded to in a thoughtful and appropriate manner. The net result may not be to the liking of every one reading this article (and probably even less palatable to those who are not) but doctors in all other specialties are undergoing broadly the same strictures. We go back to the fact that professional independence is a privilege not a right. If we do not maintain all aspects of our professional standards - and this includes CME - in a way that society wishes of us, someone else will do it for us.

Chairman, Continuing Education and Professional Development Committee.

REFERENCES

[1] ***Irvine D. The performance of doctors. I: Professionalism and self regulation in a changing world. British Medical Journal 1997; 314: 1540-1542.***

[2] ***Irvine D. The performance of doctors. II: Maintaining good practice, protecting patients from poor performance. British Medical Journal 1997; 314: 1613-1615.***

[3] ***Davis DA, Thomson MA, Oxman AD, Haynes RB. Evidence for the effectiveness of CME. Review of 50 randomized controlled trials. Journal of the American Medical Association 1992; 268: 1111-1117.***

Personal View 1:

JAMES ROCHFORD 1915-1979

by Dr J Bushman, Retired Fellow of the College.

James Rochford was a consultant anaesthetist at Barnet General Hospital when at the age of 64 he died following a cerebral haemorrhage. He trained at St Bartholomew's hospital between 1935 and 1940 and then served in the RAMC mostly in the Middle East. Here he became a Specialist in Anaesthetics and reached the rank of Major. Following his service in the Army he was a consultant anaesthetist at Barnet General and Clare Hall Hospitals. He was a man who taught by example and was a great stimulus to all his juniors. He claimed that he never had the time to read but when discussing some anaesthetic subject would give a reference which frequently included the page number in the relevant journal or textbook.

In 1954 he was one of the founder members of the North London Group of Anaesthetists and he played an active part in the group until his death. He wrote very little, a chapter on ventilators in Evans and Gray, and a paper entitled "An Electronic Time Cycled Ventilator". This was published in the BJA in 1958 with Dr Welch and Mr Winks. This was quite courageous as at that time many anaesthetists believed that "the educated hand" of the anaesthetist was superior to any form of mechanically assisted ventilation. Rochford's machine was to become the first of the Barnet ventilators. The machine was a simple time cycled minute volume divider and was very easy to use. It was not the prettiest of machine but was very robust and reliable. The machines were built by Watsons of Barnet, the microscope manufacturers, whose factory adjoined the hospital site.

This led to the development of the Barnet Mark III, an extremely versatile machine, which could be time, cycled, volume cycled or pressure cycled. At the time the first of the Barnet ventilators were produced a succession of registrars were fortunate enough to come under Rochford's tutelage. These included Hilary Howells, James Freeman, John Collis, John Bushman and Doreen Browne. Hilary Howells went on to develop the Howells ventilator, John Collis developed the Cape Minor ventilator and John Bushman, as a consultant to Philips, aided the development of the Philips AV1 and the Philips AV3 ventilators, both direct descendants of the original Barnet.

Once freed from the reservoir bag the "educated hands" at Barnet began investigating a number of other interests. These included the measurement of mean airway pressure, central venous pressure, the blood pressure. This later was a non-invasive method using the automated inflation and deflation of an oscillotonometer cuff.

A method of detecting abnormal complexes in the ECG using analogue computers was also perfected. It is doubtful if this would have occurred without Rochford's stimulation and encouragement.

Rochford always maintained excellent relationships with industry, particularly with the development engineers, and those from Watsons, BOC, Cape and Devices were frequently seen in the anaesthetic department. This was a valuable additional stimulus to the junior staff.

He was one of the first anaesthetists in the country to use bronchial lavage for the treatment of asthma and he developed a technique using a double lumen tube so that the patient had one lung ventilated while the other was washed out.

Early in the 1960's the planning and building of an ITU was begun and it was opened on January 1965. This was adjacent to the recovery area and situated close to the main theatres. The anaesthetic nurses, the recovery nurses and the ITU nurses were all part of the same team and as a result they were a very highly trained and motivated group.

The countryside around Barnet had been a centre for horse-trading and tetanus was not an uncommon sequel to penetrating injuries. Since Rochford's expertise in ventilation was well known it was natural that Barnet should be designated a centre of expertise for the treatment of tetanus. This resulted in junior staff gaining valuable experience in the long-term ventilation.

James Rochford did much to change anaesthesia from an art form to a science, particularly by adapting from technology in industry to the needs of anaesthesia. He is remembered by all who worked with him with great affection.

Personal View 2:

HOW COULD A COURSE TAKING PLACE IN A REMOTE CORNER OF UGANDA BE SO IMPORTANT?

by Dr R Hutchinson, Consultant Anaesthetist, Harare Central Hospital, Zimbabwe.

My reason for choosing this topic is that there has recently been increased recognition by many including the World Federation of Societies of Anaesthesiologists (WFSA) that most anaesthetics in Africa are given by Non-physicians. As a result if anaesthesia is to be made available and safe for "all the peoples of the world" targeting of this group educationally has high priority. As you know there is a strong anti Nurse Anaesthetist lobby particularly in the USA and Brazil. But the situation in these countries is quite different. In some countries of Africa there are virtually no Anaesthesiologists. Professor Vickers, President of the WFSA, spoke on "Physician and Non Physician Anaesthetists - Is There a Real Conflict" at the final Plenary Session of the All Africa Anaesthetic Congress in Harare in April 1997. He said that in a Third World setting Non-physicians are no threat whatsoever to Physicians. I am sure most people working in the Third World would agree. So I thought a report of a meeting in Uganda where Anaesthesia is moving forward along a quite different route to the West might be of interest to Fellows of the College.

The First National Anaesthesia and Monitoring Equipment Course took place in Kabale, Uganda, on 1-6 September 1997. It was organised by Professor Henry Bukwirwa of Makerere University, Kampala. Professor Bukwirwa is currently President of the East Africa Association of Anaesthetists and a Board Member of the Africa Regional Section of the WFSA. Faculty included two Anaesthesiologists from Uganda and three from other countries. In addition, there were six technicians from Uganda headed by the Assistant Commissioner of Health Services/Engineering.

This group was backed up by an Anaesthetic Officer involved in Equipment Maintenance from Tanzania and a Technical Training Officer from Penlon, UK who supply the EMO and OMV draw over vaporisers used in Uganda for Ether and Halothane respectively. Delegates were about 30 Anaesthetic Officers (Non-Physicians) from Uganda and one from Kigale, Rwanda. The course lasted a week and was repeated with a second group so that the input reached every hospital in the country. Working hours were 8.15 a.m. to 10.30 p.m. Why was this course so important?

This was certainly not the first course in the world devoted to equipment. One such was held in London by the Royal College of Anaesthetists in association with the Institute of Electrical Engineers in November 1996. The final session focused on Anaesthetic Simulators. The Kabale Course could not have been a greater contrast. It took place in a remote town in the mountains of

Western Uganda on the borders of Tanzania, Rwanda, and the former Zaire. The Dian Fossey Gorilla Park was only two hours drive away. Sometimes the electricity failed and once or twice water from the tap looked more like mud.

The purpose of the course was to empower users of Anaesthetic Equipment not only to understand their machines but also to maintain them and carry out simple repairs. It is well recognised that Anaesthetists should understand something of the workings of the equipment they use. It is equally well recognised that the establishment of efficient anaesthetic equipment maintenance and repair is essential. The importance of the Kabale course was that there were lectures on how the equipment works TOGETHER with opportunities for hands on stripping it down. Common faults and their causes were identified. The users were taught which of them they can rectify THEMSELVES and how to do this using very simple equipment. What was achieved as seen by an outsider?

Appropriate Technology

Anaesthetic Equipment provision in Third World African countries is developing along two distinct lines. In a number of countries anaesthetists strive to keep up with technological developments in the West. One can understand the attitude of "Nothing but the Best" for my Department/Hospital/Country. Unfortunately in practice the latest technology, if it ever gets into use, soon collapses because of the unavailability of money and skills for routine servicing and repairs. More importantly anaesthetists, often non-physicians, are trained on this "High Tec" equipment and then sent out to the periphery were it may not be available and even if it is there are no technicians to carry out the necessary maintenance. The other school of thought says that the most important facet of anaesthetic equipment is that it should be properly maintained and accurate. In addition it should be simple to use and understand so that user error is minimised. Both schools accept the need for the best possible training for the user. At Kabale, because the equipment used in Uganda is basically simple, very detailed knowledge and skills could be imparted to the users. Once you understand the obturator and slide mechanism of the OMV Halothane vaporiser it is quite easy to see how the pointer will stick if dirt gets on to the slide and more importantly how to rectify the problem with just a screw driver.

ANAESTHETISTS and TECHNICIANS were living and working together and learnt to appreciate the role of the other. Both groups could see what simple problems did not need to be referred. The opportunity was also used to up grade the peripheral hospital technicians. Appropriate ACTION to take when equipment failed was discussed by all and the mechanism of referral made clear.

All DELEGATES CONTRIBUTED. By sitting the course in the periphery delegates were on the spot all the time. They saw their leaders WORKING very hard and enjoyed doing so themselves. Everyone was encouraged to talk about his own problems and these were dealt with sympathetically. Delegates had to report and present their group work with different speakers presenting on each occasion.

Plans are already in place for FOLLOW UP to ensure that improvements in anaesthetic equipment maintenance do take place.

In the West, anaesthetists are pressed by the manufacturers to use ever more complex equipment and more expensive drugs. This is unrealistic in a Third World setting. In East Africa the problems of "High Tec" Anaesthesia have been fully appreciated. The decision has been taken to remain with simple equipment and to move forward by training its users in greater depth.

Footnote

Of great interest was the reaction to the course of the non physician Anaesthetic Officer from Kigale, Rwanda. He and one Belgian Doctor, currently away, are in charge of a programme set up by the Red Cross to train Anaesthetic Officers for Rwanda. Some of the trainees are nurses trained on the job by Aid Doctors and some are straight from school. They have a curriculum but have problems finding lecturers and have almost no books. The equipment consists of four High Tec Anaesthetic machines left behind by an Aid Agency and one EMO. There is of course no N2O. This man fully appreciates the value of simplicity in his situation and plans to try and establish training programmes based on simple equipment. Since returning from Uganda I have been asked to advise on equipment by a Physician trying to set up some sort of Anaesthetic Training in Eastern Angola. The advice was of course "Keep it Simple".

Correspondence

Sir,

THOSE MAGNIFICENT MEN AND THEIR FAILING MACHINES

From Dr J P Newell, Addenbrooke's Hospital, Cambridge.

Your Editorial in the January 1998 Newsletter neatly coincides with the FRCA "failing machine" taxiing outside the SHO departure lounge. Little wonder some trainees are as bemused as their trainers.

I agree it is time to question the purpose of the current examination. Squashing two exams into the first 36 months and leaving the rest of SpR training (soon to be 5 years?) to underdeveloped "assessments" is not the way forward. Can I highlight just two problems? The first is immediate. Trainees perceive the Final FRCA as a test of their commitment to the specialty (which it is). Rarely is it seen as the natural summation of theory and practice implied in the Syllabus. However, most SpRs (80%+) presented with modular training in the sub-specialties, and encouraged to integrate clinical practice and reading, will pass at the first attempt. That is our experience: the problem is in moving this process to the SHO years at short notice.

The second problem, as you point out, is the future. What knowledge and education will the anaesthetists need in, say, 10 years time and can or should we "examine" it with the traditional failing machine?

Adapting to change, generating new solutions and rejecting the old seem paramount. In other words, more emphasis on critical thinking and less on memory recall. I think that a dissertation, based on the trainee's declared clinical interests in the final SpR years, would be relevant.

Whatever the solution to the problem of assessment of training let us make sure that future examinations are clearly integrated with education and training; not so much a barrier, more a natural step forwards.

Sir,

CLINICAL AUDIT

From Dr A J G Gray, Norfolk and Norwich Healthcare NHS Trust

Anaesthetists are good at clinical audit (look at the number of anaesthetists who are Chairmen of their Trust audit Committees) so why does the College not do more to initiate and promote audit. For example, the annual clinical audit conference was held in London in November. Many Colleges had stands - surgeons, obstetricians, pathologists, ophthalmologists, physicians and others. There was no stand from the Royal College of Anaesthetists. Why not? Nobody available? No money? No ideas?

Secondly, the College only writes to audit leads; apparently it is too expensive to write to all Fellows individually about audit. Has the Editor of the Newsletter been asked for space for a regular bulletin on audit affairs that would reach all Fellows; it works for the pathologists. Or is there nothing to report?

I am sure there is a lot of good work going on in the Quality of Care Directorate. Can we not tell everybody, inside and outside the College, about it, and work to improve the quality of anaesthesia that we deliver.

A reply from Professor D J Hatch, Chairman, Professional Standards Committee: Dr Gray raises some interesting points about the communication of this College to it's Fellows with regard to audit and the work of the Professional Standards Committee.

I hope that he read with interest two items in the January letter about work originating from this committee: the Patient Liaison Group and the Critical Incident Study. I acknowledge that there is no regular input into the College newsletter, however this is a suggestion that we will take seriously. In the past we produced an issue of a audit newsletter that was distributed to all Fellows. Unfortunately, we had very little response or submissions from our Fellows, suggesting that we would have difficulty in producing further issues. Dr Gray's suggestion that the College has a regular section in this newsletter on clinical audit and the work of the committee therefore may have some merit.

With regard to the National Clinical Audit conference he refers to, we originally explored the possibility of having a joint stand with a number of other Colleges, as the costs for individual stands were outside our budget for this area of work. However, in the end this did not prove possible. We would hope to have a stand at the same conference next year when we will have more up to date material to demonstrate, including the anaesthetic audit recipe book that we will publish later year and the Critical Incident Study materials.

Despite a reduction in NHS(E) funding to the Colleges for audit, we will continue to ensure that audit leads within departments are kept informed about College activities in this area, in the hope that they will disseminate this information to their colleagues. The recent change of name of the Professional Standards Committee recognises the fact that although audit is important, it is only one of the ways in which the College is committed to the maintenance of standards.

Sir,

SIMULATOR TRAINING AND RESEARCH SHOULD BE COMPLEMENTARY AND COLLABORATIVE

From Drs F Forrest, M Tooley and S Mather,
Bristol Royal Infirmary.

Those of us involved in the running of the Bristol Medical Simulation Centre (BMSC), would like to comment on the recent articles on simulation that appeared in the November issue of the Newsletter.[1,2]

In his article David Wilkins accurately described the origins of BMSC and the funding of this project from the Special Trustees of the United Bristol Hospitals Trust. However, it is now ten months since the centre opened in January. A number of organisational issues have been addressed during this time. Most significant has been the reorganisation of the project which took place in June. The wholly commercial nature of the project did not sit well with the clinicians whose primary interest lay in teaching and training. From a practical standpoint these people are whole time employed and in a difficult position to deliver the commercial requirements. The NHS and University consultants now have "free" time to develop training and research programmes. We have moved forward and a number of us in Bristol have been working hard to try and make the project a success. We are now beginning to see reward for our efforts.

We have been most impressed by the work of the ACCESS team. We are certainly as committed to research and development of simulators for education as the Cambridge group. As such we hope good lines of communication will be established between the different simulator user groups whatever the simulator they are using. With another Human Patient Simulator in Scotland in the near future, and we hope a successful joint venture between Belfast and Dublin, we already have a network of interested parties.

Dr Byrne is correct that there is a paucity of research coming out of Europe at present. This may reflect the variety of simulators in use and the fact that much effort is required by these workers to develop the non-commercial systems and fund continued work with them. In the United States, some years ahead in high fidelity simulation and with two rival commercial groups, there is a considerable body of work looking not just at Crisis Resource Management for teaching but more fundamental aspects of education using a simulator. The wealth of information presented at the recent Meeting of the American Society of Anesthesiologists in San Diego reflected this.

Those of us working in this field are primarily interested and enthusiastic educators. Good and cordial communication should be the aim of this group as we try to move forward together whatever the system of simulation we are using. With the changes brought about by the introduction of the Specialist Registrar grade and the expected reduction in trainee numbers over the next few years we suspect most permanent clinicians will be distracted by questions of service delivery rather than progressive educational methods. Thus, we suspect that simulation will continue in centres with the expertise with room for many David's if only one or two Goliath's!

REFERENCES

1. ***Wilkins DG. Bristol Medical Simulation Centre. RCA Newsletter 1997;37:12-13***
2. ***Byrne JA. Simulators - David or Goliath? RCA Newsletter 1997;37:18-19***

Sir,

MEDICAL WRITERS GROUP

From Dr H T Davenport, Retired Consultant Anaesthetist, Northwood, Middlesex.

The Medical Writers Group of the Society of Authors may be of interest to Fellows who have written or are writing a medical or dental book for publication.

When the Society of Authors was founded in 1884, Bernard Shaw stated: "We all, eminent and obscure alike, need the Authors' Society". The Medical Writers Group was formed in 1979 to promote their special interests and to defend their rights.

A small permanent staff, based in Chelsea, London, give individual advice (especially contract vetting), tackle legal action of general interest, publish a journal for authors, produce a variety of Quick Guides on different aspects of authorship, arrange writing seminars and social events, and provide access to many other facilities. There are groups in Scotland and Northern England. Annual awards for outstanding books are chosen by Society Committees - the Medical Writers Group adjudicating the Royal Society of Medicine Prizes.

There is rarely much financial gain from writing or editing medical textbooks, and amicable relations with publishers are essential for the endeavour to be rewarding. Details of the types of membership, subscription rates (tax deductible) and the services provided can be obtained from 84 Drayton Gardens, London SW10 9SB (Tel: 0171 373 6642 or Fax: 0171 373 5768).

I greatly wish I had been a member of this Group and had benefited from the Society's support when I first had to deal with publishers many years ago.

Sir,

RES IPSA LOQUITUR

From Dr W Ryder, Royal Victoria Infirmary, Newcastle.

May I be permitted to reply to the article by Dr Heneghan on Res Ipsa Loquitur which appeared in the January issue of the Newsletter?

I enjoyed the article which made a valuable contribution to the understanding of those of us anaesthetists at the sharp end who are not experts in the law and who have, hither to, put too simplistic an interpretation on the principle of res ipsa.

There are, however, two or three points I would like to debate: -

1. For a "meticulous anaesthetic record" to suffice to persuade a court that there had been no negligence, I find rather disturbing. Whilst I am all in favour of proper, relevant and readable record keeping, it undoubtedly distracts the attention of the anaesthetists from the monitors and, much more importantly, from direct patient observation and care. And surely, in a critical situation the last thing you should be doing is filling in the forms meticulously? At best in that situation, an attendant should be delegated to observe, and to list in sequence, what you do and what you give to relieve the situation. This list should then form an important part of your defence evidence in place of the gap on your "meticulous" anaesthetic record and would act as a retrospective "aide memoire".

   At this point I am reminded of my three month indoctrination course in 1959 for entry to the Royal Air Force Medical Service. We were told they "didn't give a damn if the patient died, so long as we filled in all the forms"!

2. The issue of "rare and unlikely" is not quite so simple as Dr Heneghan implied. Firstly, events regarded as rare - and therefore unlikely - may not, in fact, be rare, but only rarely reported and reaching the light of day. I think this is largely what clinical incident reporting is about - i.e. to determine how frequently such an incident occurs and whether or not we need to alter our practice so as to make it rare and unlikely. How often, for instance, have any of us presented to a morbidity meeting an event we personally thought was unusual or unlikely, only to find that colleague Joe Bloggs, our senior by twenty years, had encountered and countered a similar event five times before?

Secondly, does the fact that "no cause was found" always imply rare and unlikely, and therefore no negligence? I recall a dental anaesthetic death in Cumbria some years ago in which a dentist, acting as his own anaesthetist incidentally, injected halothane IV instead of methohextone. A rare and unlikely event, surely, but very negligent nevertheless. No "cause" was found at post-mortem. In the example quoted, he actually did the same thing to his next patient before it dawned on him that something might be amiss with the "brietal". Two "rare" events in quick succession, so who needs a dental anaesthetic population of "50 million plus"?

In the actual example used by Dr Heneghan of a fit boy "dropping dead", were studies done for high viral titres to exclude acute, symptomless viral myocarditis which would not show up at post-mortem, but which is not uncommon.

It raises again a question we all ask ourselves frequently. Should we anaesthetise a patient with a history of recent viral upper respiratory infection? I can quote again from dental anaesthesia to illustrate my point. A "fit" girl of eight died under anaesthetic in a dentist's chair in Blyth, Northumberland a few years ago. Her grandmother gave the anaesthetist a history of "flu" the week before. No "cause" was found at post-mortem.

On the principle of res ipsa, and on a balance of probabilities, how would a judge find in that case?

3. That brings me to my third and last point of debate. Dr Heneghan argues that, by recording more of what we already frequently monitor (e.g. inhaled vapour concentration), or by seeking and recording other non-risky "firm evidence", we will inevitably record to "a legal standard of proof". I am not entirely convinced by this argument and not quite sure what he is implying. Is he advocating, by "legal standards of proof", that medical negligence judgements henceforth be based on evidence which is beyond reasonable doubt, rather than on a balance of probabilities? That would indeed be disturbing. In human biology and medicine, where almost everything is measured in shades of grey, and in anaesthesia and intensive care in particular, where parameters and requirements change rapidly and from moment to moment, I would hate to see more rigid standards of evidence applied than obtain at present.

May I be permitted one final and cynical thrust? Dr Heneghan clearly rejoices in the statement that "Trial by Battle" was abolished in 1819 and that judges can now judge only on the basis of witness evidence. It seems to me that the British judicial system has little to do with quality or quantity of evidence and justice and everything to do with who is the more powerful adversary (advocate, Mr Heneghan). What is that but "Trial by Battle"?

Please keep the interesting articles coming Dr Heneghan - if you are not too busy seeking election to the College Council!

A reply from Dr C P H Heneghan: Dr Ryder makes the point that in a critical situation we should not be filling in forms: I agree, and did say that we should only be gathering more or better evidence when the risk to the patient is not increased. Otherwise, recording should be retrospective, even if it increased the risk to our reputations.

I do not wish to imply that "rare" is easy to define, but to point out that whilst we may accept that rare things occur regularly - if infrequently - a judge may not, and may need convincing.

"Legal Standard of Proof" does not mean beyond reasonable doubt: that is the criminal standard of proof (perhaps we should not resist its introduction, as it usually operates in favour of the Defendant). I merely mean that a record intended solely as an aide memoire may have insufficient detail to form a record which a judge would have no hesitation in accepting. Remember that a court's purpose is to test the evidence and it may find the evidence wanting if it is apparently full of gaps.

Finally, I make no apology for delighting in the abolition of Trial by Battle, though my surprise at the abolition being delayed until 1819 was what I meant to express. However, I would expect Dr Ryder's view, that British justice has little to do with evidence, to be altered by spending some time in the courts. He would not see an American media trial here, he would see decisions based on evidence. He should remember that if the evidence does not represent the facts, it is not the Judge's fault. As is said of democracy, so of the adversarial system: it may not be much good, but everything else is worse.

Sir,

INTENSIVE CARE TRAINING FOR ANAESTHETISTS

From Dr P Radford, on behalf of the Specialty Training Committee for Anaesthetics, South Thames (West)

The recommendations of the Intercollegiate Board are the culmination of years of work by those working in the field and at College level. It is with regret, therefore, that we do not see how they can work. We agree with the doubts expressed by Fletcher, Ridley and Burchett in the January Newsletter.

There are three serious gaps between what is recommended and what is possible (or even desirable).

Firstly, there will not be enough recognised training posts for the senior house officers form the acute specialties in the limited number of accredited units.

Secondly, training scheme organisers across the country know that it takes two years to deliver the modular training that the College training guide expects us to provide in the first specialist registrar year: there is no "spare" year to fit in 6 months of medicine and 6 months of intensive care.

Finally, few anaesthetists regard a specialist registrar programme of with only two years in anaesthesia as adequate for a CCST in anaesthetics.

Report of Meetings of Council

At a meeting of Council held on **Wednesday, 17 December 1997**, Professor P D Wall was presented with the Dudley Buxton Prize.

Professor P D Wall

A summary of his Citation given by Dr D M Justins: The Dudley Buxton Prize is awarded triennially for meritorious work in anaesthesia or in a science contributing to the progress of anaesthesia. The Prize commemorates Dudley Buxton (1855-1931) who was anaesthetist to University College Hospital in Gower Street. There are some intriguing links between Dr Dudley Buxton and Professor Patrick Wall who is to receive the Dudley Buxton Prize today. The first is Gower Street. Pat Wall was Professor of Anatomy at University College, London (UCL) also in Gower Street from 1967-1990. The route to UCL was by Middlesex Hospital Medical School with graduation in 1948. Between 1948-1959 Pat Wall worked at Yale, University of Chicago, Harvard and the Massachusetts Institute of Technology (MIT) in Boston. From 1959-1967 he was Professor of Physiology at MIT. In 1967 he returned to take up the post at UCL. In 1972 he added Visiting Professor at the Hebrew University, Jerusalem a post which he still holds. Since his retirement from UCL Pat Wall has continued active research as Professor Emeritus of Physiology on the St Thomas' Hospital campus of UMDS (United Medical and Dental School) and he has also found a home for his editorial activities here at the Royal College of Anaesthetists.

Pat Wall has made a massive contribution to the science which underlies anaesthesia. More than 300 papers spanning 50 years bear witness to this contribution.

Dudley Buxton stated that the anaesthetist must be scientifically as well as practically educated in his art. More than anyone else Pat Wall has been responsible for bridging the gap between the basic sciences and the clinical practice of pain management.

Dudley Buxton was one of the first to recognise the influence of psychological factors on patient well being. Likewise, Pat Wall has always recognised that pain is a multidimensional problem and he has collaborated with scientists and clinicians from many disciplines throughout his career.

Undoubtedly his most famous collaboration has been with a psychologist Ron Melzack, a psychologist-cum-physiologist and Pat Wall, a medically qualified scientist produced the pivotal paper of 20th century pain research. "Pain mechanisms: a new theory" published in Science in 1965. In 1962 they had published in Brain a more general theory on sensory mechanisms which had rather escaped notice but the Gate Theory was revolutionary.

The Gate was a theory but the ideas were subsequently given strong support by basic and clinical research, much of it involving Pat Wall. Although the Gate has evolved into a complex neuromodulatory system of facilitatory and inhibitory controls, our knowledge is still in the final analysis, based on that initial theory; and it was that theory which was the prime stimulus for the exciting explosion in pain research which has occurred in the last 30 years. Pain has moved out of the shadows of neglect and into the limelight where it has been recognised as a major clinical problem for virtually every branch of clinical medicine and also as a suitable subject for basic research. Pat Wall has argued persuasively that relief from pain is a basic humanitarian right.

With Sweet the neurosurgeon, Pat Wall was able to apply the concepts of the Gate Theory to produce a clinically useful treatment. Transcutaneous Electrical Stimulation (TENS) which is widely used today. In a more recent example of applying basic science to clinical problems Pat Wall in 1988 wrote an editorial in the Journal Pain which promoted the concept of pre-emptive analgesia and the subsequent debate has encouraged anaesthetists to look more closely at the way in which they manage acute pain.

Very importantly Pat Wall also advocated the multi-professional approach to pain management. The International Association for the Study of Pain (IASP) has done so much to promote this collaborative approach to pain research and management and Pat Wall was one of those enlightened individuals responsible for founding the organisation.

Dudley Buxton wrote a textbook "Anaesthetics: their uses and administration" which ran to six editions from 1888 to 1920. Pat Wall along with his friend Melzack, has edited the "Textbook of Pain" which is the standard major textbook for basic scientists and clinicians alike. The fourth edition is in preparation. As in Buxton's book there is an emphasis on the need to understand the basic science in order to begin to understand the clinical problems. Pat Wall was the founding editor of the Journal Pain in 1967 and still continues as Editor-in-Chief. Under his stewardship this Journal has assumed the pre-eminent place in pain literature by only accepting papers of the very highest scientific standard. Pain has published the work of many anaesthetists thereby recognising the major contribution that anaesthetists make to research into both the mechanisms and management of pain. Pat Wall is a member of the Research Committee of the Royal College of Anaesthetists.

Pat Wall has never been afraid of engaging in intellectual combat. His presence greatly enlivens any scientific meeting. He has championed unfashionable causes such as the medical use of cannabinoids and he has made a public defence of ethically conducted animal research. He is a member of the Scientific Committee of the RSPCA. He is a man who has achieved greatness yet he is approachable and genuinely interested in the ideas of others. In fact he thrives on discussion and is always bursting with ideas and infectious enthusiasm. His thinking is imaginative and leaps way beyond any narrow confines. He is capable of looking at something from a totally unexpected angle and has very wide-ranging interests.

Professor Patrick Wall has received honours from all around the world and he is a Fellow of the Royal Society. He has indeed done truly meritorious work in science contributing to the progress of anaesthesia and is richly deserving of the Dudley Buxton Prize.

The following were appointed/re-appointed **COLLEGE TUTORS**:

Oxford Region
Dr A Kapila, Royal Berkshire & Battle Hospitals, Reading
[in succession to Dr C Verghese]

North Thames (West)
Dr E Whitehead, Ealing Hospital
[in succession to Dr M M Meurer-Laban]

North Thames (Central)
Dr G Timmins, Colchester General Hospital
[in succession to Dr S I P Mackenzie]
Dr P Dodd, King George Hospital, Goodmayes
[in succession to Dr M Y Khan]

North West
Dr S Costigan, Furness General Hospital
[in succession to Dr V Govenden]

South West
Dr J Dunnet, Frenchay Hospital, Bristol
[in succession to Dr A Manara]

South Thames (East)
*Dr J B Broadfield, King's College Hospital

Wales
Dr P Baynham, Prince of Wales Hospital, Merthyr Tydfil
[in succession to Dr B Jenkins]

West Midlands
*Dr I P Hine, Hereford Hospitals NHS Trust
*Dr R D Patel, New Cross Hospital, Wolverhampton

The following were awarded **CERTIFICATES OF COMPLETION OF SPECIALIST TRAINING**:

Northern and Yorkshire
Dr Andrew John Berrill
Dr Paul Nicholas Charlton
Dr Hans Klein
Dr Susan Lesley Lindsay
Dr Nicola Jane Snook

Trent
Dr Brynley Roy Baxendale
Dr Michael Andrew Norris
Dr Paul Edington Shannon
Dr Howard Michael Thompson
Dr Guy Richard Quentin Veall
Dr John Edward Hendon Ward
Dr Ian James Wrench
Dr Richard Peter Wroth

North Thames (West)
Dr Stephen James Bates
Dr John Roy Fernandes
Dr Charles Robert Garcia-Rodriguez
Dr Ayad Abdul Karem Shakir
Dr Alison Elizabeth Shawe

North Thames (Central)
Dr Stephen Gerard Brosnan

North Thames (East)
Dr Stylianos Panayiotou
Dr Jeremy John Radcliffe

South Thames (East)
Dr Helen Maria Daly
Dr Susan Joanna Milroy
Dr Paul David Noble
Dr Babaseyi Oyedele Oyesola
Dr Jacqueline Sarah Porter

South Western
Dr Nicholas Julian Kennedy
Dr Andrew Keith McIndoe
Dr Emert White

West Midlands
Dr James Ernest Craggs
Dr Craig William Stenhouse

North Western
Dr Gerard Andrew Dempsey
Dr Robert Hamish Paton
Dr Mansoor Ahmad Sabar

Wales
Dr Amisha Mehta

Aberdeen
Dr Alan Donald Thomas

Edinburgh
Dr Joyce Cameron Stuart

Glasgow
Dr William John MacRae
Dr Jennifer Susan Walker

****Re-appointment.***

At a meeting of Council held on **Wednesday, 21 January 1998**, the following were appointed/re-appointed **COLLEGE TUTORS:**

North Thames (East)
Dr S Harrod, St Bartholomew's Hospital
[in succession to Dr H Hackett]
Dr J Durcan, Broomfield Hospital, Chelmsford
[in succession to Dr N Huddy]
Dr F Ogunyemi, Newham Hospital

Provisional Educational Programme 1998/99

MEETINGS

GOLDEN JUBILEE MEETING

18/19 MARCH 1998

A two day Golden Jubilee meeting on **"Progress in Anaesthesia"** to be held at the Royal College of Surgeons of England. The Joseph Clover Lecture and AGM will be held on the afternoon of 18 March and the Golden Jubilee Dinner will be held in the evening at The Guildhall in the City of London.

TRAINING PARAMEDIC TRAINERS

18 MAY 1998

[Please note the change of date]

A comprehensive one day Seminar to be held in the Lecture Theatre at the College.

CONTINUING MEDICAL EDUCATION DAY

10 OCTOBER 1998

A one day meeting organised jointly by the Association of Anaesthetists of Great Britain and Ireland and the Royal College of Anaesthetists to be held in London. The meeting will consist of 18 lectures held in 3 different lecture theatres, enabling participants to attend a total of 6 presentations in the course of the day.

SYMPOSIUM

5-6 NOVEMBER 1998

A two day meeting on **"Pharmacology in Anaesthesia - 50 Years on"** to be held at the Institute of Engineers in London.

ANNIVERSARY FORUM

17 MARCH 1999

A one day meeting on **"Endocrine Problems and Anaesthesia"** to be held at the Royal College of Surgeons of England. The Frederic Hewitt Lecture and AGM will be held in the afternoon and the Annual Dinner will be held in the evening *(venue to be confirmed)*.

SCIENTIFIC MEETING

7 MAY 1999

A one day meeting on **"The Respiratory System in Anaesthesia and Intensive Care - The Lung, Airway Diaphragm and Trauma"** to be held at the Institute of Engineers in London.

TRAINING PARAMEDIC TRAINERS

24 MAY 1999

A comprehensive one day Seminar to be held in the Lecture Theatre at the College.

COURSES

BASIC SCIENCES FOR ANAESTHETISTS COURSE

19-30 JANUARY 1998

This course is intended for those studying for the Primary Examination and consists of two weeks of full time lectures on anaesthetics and those aspects of physiology, pharmacology and statistics that are of interest to anaesthetists. Lectures will take place from 09.30 to 17.30 Monday to Friday.

FINAL COURSE

16 FEBRUARY-6 MARCH 1998

This course is intended for those studying for the Final Examination and consists of three weeks of full time lectures on anaesthesia.

COURSE ON CURRENT TOPICS IN ANAESTHESIA

8-12 JUNE 1998

This course consists of lectures, each of which is followed by ample time for discussion. It is intended for Consultants and Senior Anaesthetists who feel they may benefit from a refresher course in the latest techniques.

BASIC SCIENCES FOR ANAESTHETISTS COURSE

6-17 JULY 1998

This course is intended for those studying for the Primary Examination and consists of two weeks of full time lectures on anaesthetics and those aspects of physiology, pharmacology and statistics that are of interest to anaesthetists. Lectures will take place from 09.30 to 17.30 Monday to Friday.

FINAL COURSE
21 SEPTEMBER-9 OCTOBER 1998

This course is intended for those studying for the Final Examination and consists of three weeks of full time lectures on anaesthesia.

COURSE ON CURRENT TOPICS IN ANAESTHESIA
9-13 NOVEMBER 1998

This course consists of lectures, each of which is followed by ample time for discussion. It is intended for Consultants and Senior Anaesthetists who feel they may benefit from a refresher course in the latest techniques.

BASIC SCIENCES FOR ANAESTHETISTS COURSE
25 JANUARY-5 FEBRUARY 1999

This course is intended for those studying for the Primary Examination and consists of two weeks of full time lectures on anaesthetics and those aspects of physiology, pharmacology and statistics that are of interest to anaesthetists. Lectures will take place from 09.30 to 17.30 Monday to Friday.

FINAL COURSE
15 FEBRUARY-5 MARCH 1999

This course is intended for those studying for the Final Examination and consists of three weeks of full time lectures on anaesthesia.

COURSE ON CURRENT TOPICS IN ANAESTHESIA
7-11 JUNE 1999

This course consists of lectures, each of which is followed by ample time for discussion. It is intended for Consultants and Senior Anaesthetists who feel they may benefit from a refresher course in the latest techniques.

Meetings are open to all anaesthetists and other interested medical practitioners. Application forms will be sent before all MEETINGS to Fellows and Members (paying the annual subscription) of The Royal College of Anaesthetists.

Application forms for COURSES may be obtained by writing to the Education Department at the Royal College of Anaesthetists, 48/49 Russell Square, London WC1B 4JY (Direct Tel: 0171 813 1888 or e-mail: educ@rcoa.ac.uk).

Payment for all courses and meetings can now be made by credit card.

Outside Meetings

Association of Anaesthetists of Great Britain and Ireland

15 January 1998 Consultants Update Day (Queen Elizabeth II Centre, London). Morning Session: Association of Paediatric Anaesthetists. Afternoon Session: Plastic Surgery and Burns Anaesthetists.

16-17 January 1998 Winter Scientific Meeting (Queen Elizabeth II Centre, London). Specialist Session: European Society of Regional Anaesthesia (Great Britain and Ireland Section).

15-17 April 1998 Group of Anaesthetists in Training Annual Scientific Meeting and Linkman Conference (Nottingham).

Further information can be obtained from: Mrs Louise Watts, Ohmeda Educational Co-ordinator, Association of Anaesthetists of Great Britain and Ireland, 9 Bedford Square, London WC1B 3RA (Tel: 0171 631 1650).

Appointment of Fellows to Consultant and Similar Posts

REAH Dr G
Calderdale Healthcare Trust, Halifax.

Deaths

The College was saddened to note the deaths of the following Fellows:

BOLLEN Dr A R
Sale, Cheshire.

D'SOUZA Dr C A
Upton, Wirral.

HOLLOWAY Dr M H W
Minchinhampton, Gloucester.

KANE Dr G M
Eggington, Bedfordshire.

LOPES-SOARES Dr E
Lisboa, Portugal.

Dr R P Harbord MD FRCA

Dr Harbord, now of New Knoxville, Ohio, USA, has presented to the College a painting of the Ether Dome in Boston. The painting, by Dr Harbord, was made from a photograph of the Ether Dome taken in 1962. Dr Harbord was the first part-time Demonstrator in the University of Liverpool and after serving in mobile units in the RAMC during the Second World War he became the first full-time Reader and Head of Department of Anaesthesia in the University of Leeds before moving to the USA.

Order Form

LEAD CRYSTAL GLASSWARE

NIGHT CAP SET

I would like to order .... set(s) of the Night Cap Decanter and two glasses at a cost of **£34.10 (incl. VAT) plus £3.50 p&cp.**

I enclose £ .... ***[Please make cheques payable to "The Royal College of Anaesthetists"]***

DINNER DECANTER SET

I would like to order .... set(s) of the Dinner Decanter and two glasses at a cost of **£75.35 (incl. VAT) plus £3.50 p&cp.**

I enclose £ .... ***[Please make cheques payable to "The Royal College of Anaesthetists"]***

NAME: .... CONTACT TEL: ....

ADDRESS: ....

....

....

....

Please debit my credit card VISA/DELTA/MASTERCARD or SWITCH (Please circle) with £ ....

CARD NO: .... EXPIRY DATE: ....

ISSUE No *(Switch only)*: .... CARDHOLDER'S NAME: ....

DATE: .... CARDHOLDER'S SIGNATURE: ....

PLEASE DETACH HERE

Please complete and return to:
Mrs Eva Lazari
Royal College of Anaesthetists
48/49 Russell Square
LONDON WC1B 4JY

TO CELEBRATE THE COLLEGE'S GOLDEN JUBILEE

Lead crystal glassware handcut and engraved with the Royal College of Anaesthetists crest 1948–1998

The Decanter and glasses come in two sizes:

NIGHT CAP SET
Decanter: 14cm high
Two whiskey glasses: 6cm high **Price: £34.10 (incl. VAT) plus £3.50 p&p**

DINNER DECANTER SET
Decanter: 20cm high
Two whiskey glasses: 8cm high **Price: £75.35 (incl. VAT) plus £3.50 p&p**

Please send the order form (see opposite page) together with your cheque made payable to the **"Royal College of Anaesthetists"** to Mrs Eva Lazari at the Royal College of Anaesthetists, 48/49 Russell Square, London WC1B 4JY.
Please note that your order may be despatched direct from Burns Crystal Glass Ltd.

GlaxoWellcome

The colour cover of this publication is supported by a grant from GlaxoWellcome

The operation should be the start of her recovery, not her sickness.

Zofran™
ondansetron

Trust it to deliver

PRESCRIBING INFORMATION:
USES Postoperative nausea and vomiting. **DOSAGE** ***Adults:*** Prevention – 4mg i.v. or i.m. at induction, or 8mg orally one hour before anaesthesia followed by two further doses of 8mg at 8 hourly intervals, or 16mg orally one hour before anaesthesia. Treatment – 4mg i.v. or i.m. ***Children:*** Prevention and treatment 0.1mg/kg i.v. up to a maximum of 4mg. ***Moderate or severe hepatic impairment:*** maximum daily dosage 8mg. **CONTRA-INDICATIONS** Hypersensitivity. **PRECAUTIONS** Pregnancy. Lactation. **SIDE EFFECTS** Headache, constipation, hiccups, sensation of warmth or flushing. Transient rises in aminotransferases. Rarely hypersensitivity (including anaphylaxis), blurred vision, dizziness, hypotension, bradycardia, chest pain, cardiac arrhythmias, involuntary movement disorders and seizures (for which there is no known pharmacological explanation). **PRESENTATIONS** Zofran Flexi-Amp plastic ampoules containing 4mg or 8mg ondansetron (0004/0375, 4mg x 5 ampoules £33·75; 8mg x 5 ampoules £67·50). Zofran 4mg Tablets containing 4mg ondansetron (10949/0110, 4mg x 30 tablets £121·50). Zofran 8mg Tablets containing 8mg ondansetron (10949/0111, 8mg x 10 tablets £81·00). Zofran Syrup, 4mg ondansetron in 5ml (10949/0246, 50ml £40·50). **Product licence holders:** Glaxo Wellcome UK Limited, Stockley Park West, Uxbridge, Middlesex UBII IBT, Glaxo Operations UK Limited, Greenford Road, Greenford, Middlesex UB6 OHE. Further information is available on request from: Glaxo Wellcome UK Limited, Stockley Park West, Uxbridge, Middlesex UBII IBT. Tel: 0181-990 9444. POM Zofran and Flexi-Amp are trade marks of the Glaxo Wellcome Group of Companies. Date of preparation: October 1997.

GlaxoWellcome

BRITISH JOURNAL OF ANAESTHESIA

EDITORIAL BOARD

Editor

G. Smith, *Professor of Anaesthesia, University of Leicester*

Editor of Educational Reviews

L. Strunin, *BOC Professor of Anaesthesia, London Hospital Medical College, University of London*

A. P. Adams, *Professor of Anaesthetics, United Medical and Dental Schools of Guy's and St Thomas's Hospitals, University of London*
G. Drummond, *Consultant Anaesthetist, Royal Infirmary, Edinburgh*
F. R. Ellis, *Professor of Anaesthesia, University of Leeds*
W. Fitch, *Professor of Anaesthesia, University of Glasgow*
G. M. Hall (Chairman), *Professor of Anaesthesia, University of London*
M. J. Halsey, *Clinical Research Centre, Harrow*
D. J. Hatch, *Vice President, Royal College of Anaesthetists*
C. J. Hull, *Professor of Anaesthesia, University of Newcastle*
J. M. Hunter (Secretary), *Senior Lecturer in Anaesthesia, University of Liverpool*
W. W. Mapleson, *Emeritus Professor of the Physics of Anaesthesia, University of Wales College of Medicine*
R. D. Miller *Professor of Anesthesia, University of California, San Francisco*
J. Norman (Treasurer), *Professor of Anaesthetics, University of Southampton*
I. Power, *Senior Lecturer in Anaesthesia, University of Wales College of Medicine*
C. S. Reilly, *Professor of Anaesthesia, University of Sheffield*
J. W. Sear, *Clinical Reader in Anaesthesia, University of Oxford*
A. A. Spence, *President, Royal College of Anaesthetists*
J. E. Utting, *Professor of Anaesthesia, University of Liverpool*
J. A. W. Wildsmith, *Consultant Anaesthetist, Royal Infirmary, Edinburgh*

Associate Editors

C. D. Hanning, *Senior Lecturer, University of Leicester*
J. A. Langton, *Senior Lecturer, University of Leicester*
D. J. Rowbotham, *Senior Lecturer, University of Leicester*

Technical Editors

Ms L. Gough, B.SC., *13 Belgrave Place, Kempton, Brighton, E. Sussex BN2 1EL*
Mrs S. E. Lowry, PH.D., *19 Maiden Erleigh Drive, Reading, Berks RG6 2HP*

Subscribers' changes of address: All Fellows of the College, worldwide, should notify changes of address directly to the Royal College of Anaesthetists. All other subscribers, worldwide, should notify changes of address directly to Professional & Scientific Publications. All editorial matters should be addressed directly to the Editor. (Instructions below, to U.S. Postmasters, are *not* for the attention of subscribers.)

British Journal of Anaesthesia ISSN 0007-0912 (monthly). Second Class postage paid, Rahway N.J. **Postmaster**: send address corrections to B.J.A. c/o Mercury International Ltd, Inc., 2323 Randolph Avenue, Avenel, N.J. 07001. (U.S.A.

EUROPEAN SOCIETY OF ANAESTHESIOLOGISTS

Cover letter for abstract submission 1994

This letter must be filled out completely and submitted with each abstract (or the abstract will be rejected for technical reasons).
All abstracts and completed cover letter must be post stampled no later than October 1, 1993 in an envelope with stiff cardboard.

PLEASE TYPE

1. TITLE OF ABSTRACT:

2. NAME OF AUTHORS: (Maximum admitted: 5)

a. Presenting author ....
b. ....
c. ....
d. ....

3. NAME, CITY AND STATE OF INSTITUTION (ONLY 1!) AS IT WILL APPEAR IN THE PROGRAMME:

4. SESSION PREFERENCE (check only 1)

☐ Epidemiology in anaesthesia and intensive care
☐ Outpatient anaesthesia
☐ Patient safety, equipment, monitoring and computers
☐ Clinical circulation
☐ Experimental circulation
☐ Respiration
☐ Metabolism, nutrition, endocrinology
☐ Neurosciences
☐ Local and regional anaesthesia
☐ Pharmacology
☐ Paediatric anaesthesia and intensive care
☐ Obstetric anaesthesia
☐ Intensive care medicine
☐ Resuscitation and emergency medicine
☐ Acute and chronic pain management

5. PRESENTATION PREFERENCE ☐ Verbal ☐ Poster ☐ Indifferent

6. STATEMENTS (to be completed and signed on the reverse side)

7. FOR ESA CORRESPONDENCE:

NAME AND ADDRESS OF THE PRESENTER

Tel.:

Fax:

STATEMENTS

The purpose of this directive is not to limit the number of presentations, but to avoid duplicate presentation to major meetings of anaesthesiologists

This work will not

—*be presented* to a large English-speaking meeting of anaesthesiologists prior to the 1994 ESA meeting;
—*appear* in another form at that meeting;
—*be published* prior to the 1994 meeting in whole or abstract form in an indexed journal.

A. *Human studies* (to be signed by Senior Author if human subjects were used). I have satisfied the requirements of my institution or organization regarding the use of human subjects in research.

B. In consideration of the **European Society of Anaesthesiologists** taking action in reviewing and editing my/our submission, the author(s) undersigned hereby transfer(s), assign(s), and otherwise convey(s) all copyright to ownership in said work to the European Society of Anaesthesiologists in the event said work is published by the Society. I/We understand that this copyright assignment applies only to the abstract submitted herewith and does not apply to, or prevent, subsequent publication elsewhere of a full manuscript relating to the subject matter of such abstract.

____
(signature Presenter)

____
(signature Senior Author)

GUIDE FOR AUTHORS
(English abstracts only)

ESA would like to encourage in every way possible the submission of abstracts from non-English speaking doctors. With this in mind, we ask that you please try to ensure that the abstract you submit uses the clearest English. We will try and help by correcting the English where necessary, but *you* must help us by sending papers that have been corrected as much as possible at source. We look forward to receiving your abstract papers for the ESA Congress in 1994.

Accepted abstracts will be published as a supplement to the February 1994 issue of *BJA—International Journal of Anaesthesia.* All abstracts which follow the guidelines presented below will be read by three blinded reviewers. Reproduction of accepted abstracts will be made by photoreduction to 80% of the original size. Abstracts cannot be retyped and thus will appear as they are submitted. It is therefore extremely important that you comply with the following simple rules.

1. The size and layout of abstracts are shown below. Line-spacing, subtitles, fonts (Times, Roman or similar) and font size (11–12/inch) should follow the style of the abstracts in this Supplement. Dot matrix printing is not allowed. If you have printing problems, submit your abstract on a 3.5 inch diskette using Words or Words for Windows version 2.0.
2. One figure or one table included within the borders of the abstract is allowed.
3. A maximum of three references may be included and should be listed at the end of the abstract in numerical order, and in accordance with the layout presented in the abstract example. They should be referred to in the text by corresponding numbers.
4. Relevant key words should be supplied on a separate page containing the title of the abstract and the list of authors to be used for the annual *BJA* index. Only the original of this page is needed.
5. Use the SI system for all data.
6. Submit one original, three unblinded and three blinded copies of your abstract. References which could unblind the abstract should also be removed.
7. Abstracts from non-English speaking countries should be checked as far as possible for linguistic errors before submission.
8. Only abstracts post stamped, or sent by courier, no later than October 1, 1993 will be considered for review.

The following absolute restrictions apply:

1. Abstracts submitted by fax are not accepted.
2. Abstracts which are not readable in English, will regrettably be returned without review.
3. Abstracts which are not complete, or abstracts that do not comply with the layout rules, will regrettably be returned.

Submit abstracts to:

Dr Sebastian Reiz, Department of Anaesthesia & Intensive Care, University of Umea, S-901 85 Umea, Sweden (Fax +46 90 131388).

Authors of rejected abstracts will be notified by mail (or by fax, if a fax number is supplied on the cover letter) approximately six weeks after receipt of the abstract. Authors of accepted abstracts will be notified approximately one month later.

TITLE:

AUTHORS:

AFFILIATION:

Subtitles:

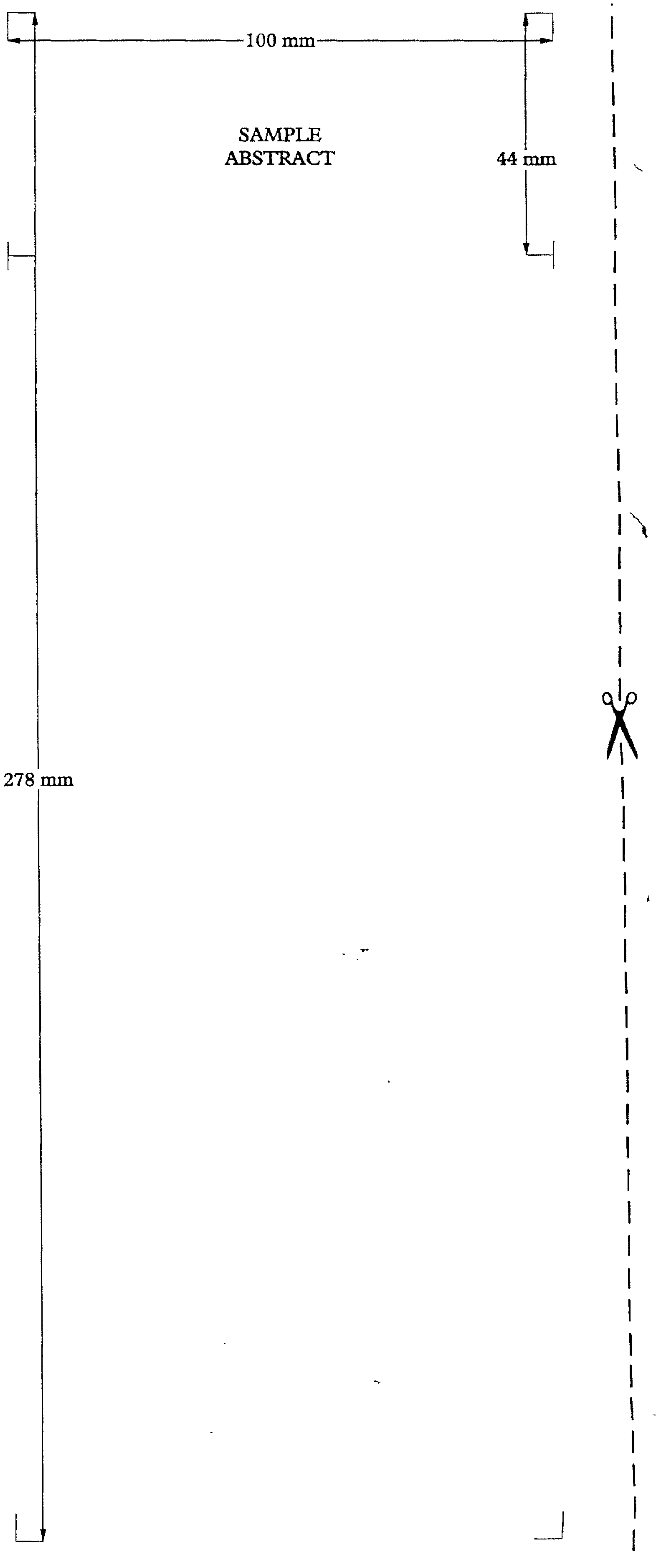
Background & goal of study:

Materials & methods:

Results & discussion:

Conclusion(s):

References:



EUROPEAN SOCIETY OF ANAESTHESIOLOGISTS FOUNDING CONGRESS

12–16 May, 1993

PROGRAMME

10.40–12.10 Friday 14 May, 1993—Léopold II B
EPIDEMIOLOGY IN ANAESTHESIA AND INTENSIVE CARE (POSTER SESSION)

ABSTR. NO.

A new clinical score to predict difficult intubation A.1
J. Arné, P. Descoins, D. Bresard, J. Ariès and J. Fusciardi

An audit of the incidence and costs associated with post operative nausea and vomiting (PONV) following major gynaecological surgery in an inpatient population A.2
R. W. Morris, E. Ernst, D. J. Greaves, D. J. Layfield and R. F. Michael

Anesthesia for patients ≥ 90 years of age in emergency hip surgery A.3
S. Eleftheriadis, H. Kuppe, K. F. Klotz and P. Schmucker

A survey of sleep problems in surgical patients A.4
L. Beydon, A. Rauss, F. Lofaso, A. Harf and F. Bonnet

Indications for coronary revascularisation in vascular surgical patients A.5
M. Gosgnach, P. Coriat, M.-H. Fleron, M. Bertrand and P. Viars

Does routine preoperative coronary angiography modify outcome after aortic surgery? A.6
M. Gosgnach, M. Bertrand, A. Pironkov, P. Coriat and P. Viars

Outcome for patients in intensive care unit with acute renal failure requiring dialysis A.7
E. Ejlersen, M. B. Jensen and K. Eliasen

A national database for intensive care medicine in Sweden A.8
M. Karling

10.40–12.10 Thursday 13 May, 1993—Astrid
OUTPATIENT ANAESTHESIA (ORAL SESSION)

A comparison of midazolam and midazolam plus fentanyl for colonoscopy A.9
H. Dupont, J.-B. Nyarwaya and K. Samii

Evaluation of saccadic eye movements as an objective test during recovery from anaesthesia A.10
O. Paut, J.-L. Vercher, O. Blin, D. Mestre and J. Camboulives

Alizapride does reduce pain on injection of propofol: Comparison with lidocaine A.11
G. Zaouk, E. Gilbart, A. Dubois, D. Jacobs and E. Balatoni

Ondansetron 4 mg vs droperidol 1.25 mg in the prophylaxis of postoperative nausea and vomiting after alfentanil-supplemented inhalation anaesthesia A.12
E. Alon, P. M. Lenzlinger and T. Pasch

Double-blind comparison of ondansetron, droperidol and saline for prevention of nausea & vomiting after orthopaedic surgery A.13
T. J. Gan, R. Collis and M. Hetreed

Comparison of ondansetron, metoclopramide and droperiodol for the prophylaxis of emetic symptoms after gynecological laparoscopic procedures A.14
C. Geiger, O. Kick, H. Böhrer, J. Motsch and E. Martin

8.40–10.10 Friday 14 May, 1993—Dynastie A
PATIENT SAFETY, EQUIPMENT, MONITORING AND COMPUTERS (ORAL SESSION)

Clinical evaluation of the calibration of noninvasive continuous blood pressure measurement devices by means of oscillometric blood pressure measurements A.15
J. R. de Jong, H. H. Ros and J. J. de Lange

Technical aspects of jugular bulb oximetry A.16
C. De Deyne, J. Poelaert, J. Decruyenaere and F. Colardyn

Is correlation of arterial and end-tidal carbon dioxide pressure during inhalation anaesthesia better with laryngeal mask as compared to face mask? A.17
D. Ivens and C. Verborgh

Cardiac output (CO) measurement: Comparison of esophageal Doppler (ED) vs thermodilution (TD) A.18
J. Y. Lefrant, J. E. de La Coussaye, G. Aya, G. Saïssi and J. J. Eledjam

Cardiac output determined from pulmonary gas exchange A.19
B. Österlund, G. Johansson and S. Reiz

Preservation of humidity and heat of respiratory gases in patients with minute ventilation > 10 l/min A.20
C. Martin, L. Papazian, G. Perrin, P. Saux and F. Gouin

CLINICAL CIRCULATION

13.40–15.10 Wednesday 12 May, 1993—Astrid
Transesophageal echocardiography, myocardial ischaemia detection (Oral session)

ABSTR. NO.

Tolerance of preoperative transesophageal echocardiography in patients scheduled for aortic surgery........ A.21
M. Gosgnach, F. Le Bret, N. Smail, M. Beaussier and P. Viars

Dipyridamole-TEE and 24 h Holter-ECG as preoperative screening tests for coronary artery disease in patients with abdominal aortic aneurysm........ A.22
M. Östman, M. Karling, K. Karp, D. Teien and S. Reiz

Evaluation of haemodynamic indices of myocardial ischaemia in patients with coronary artery disease (CAD)........ A.23
P. Hohner, G. Johansson, S. Häggmark, V. Mehta and S. Reiz

The use of the cusum plot for determination of myocardial ischaemia threshold during atrial pacing in patients with coronary artery disease........ A.24
S. Reiz, G. Johansson, P. Hohner and S. Häggmark

Evaluation in intensive care of the fraction area change obtained by automatic border detection........ A.25
N. Liu, P. Catoire, J. Rosso, M. Saada and F. Bonnet

Sensitivity and specificity of mechanical and electrocardiographic myocardial ischaemia (MI) monitoring techniques........ A.26
P. Hohner, V. Mehta, M. Saada, S. Häggmark, E. Jansson, G. Johansson and S. Reiz

15.40–17.10 Wednesday 12 May, 1993—Astrid
Anaesthesia and intensive care related to cardiac surgery (Oral session)

Pulmonary and systemic vascular effects of isoproterenol, nitroglycerin and prostaglandin E1 early after cardiac operations in patients with pulmonary hypertension........ A.27
J. Alvarez, M. L. Camara, J. Cortinas, J. Cortes and A. Aris

Echocardiographic study of the induction with a low-dose of sufentanil for coronary artery surgery........ A.28
N. Bromberg, C. Decoene, E. Chammas, A. Pol and R. Krivosic-Horber

Gastric mucosal perfusion is better preserved during cardiac surgery when isoflurane rather than enflurane or propofol is used to maintain anaesthesia........ A.29
M. Mythen, D. Browne, C. Hamilton-Davies and A. Webb

Propofol/fentanyl-anesthesia in patients with highly depressed cardiac function........ A.30
H. Rauch, F. Fleischer, R. Haußmann, B. Böttiger and E. Martin

Accuracy of processed auditory evoked response in predicting movement during cardiac surgery........ A.31
H. Kuppe, K.-F. Klotz, S. Eleftheriadis, H. Gehring and W. Gerling

13.40–15.10 Thursday 13 May, 1993—Astrid
Clinical circulation—General I (Oral session)

Cerebral blood flow velocities (CBFV) during anaesthesia for gynaecological laparoscopic surgery........ A.32
J. C. Granry, C. Monrigal, J. P. Jacob and J. P. Monrigal

Neuroendocrine changes during pneumoperitoneum for laparoscopic cholecystectomy........ A.33
J. Joris and M. Lamy

Influence of pneumoperitoneum and posture on hemodynamic and stress response during anaesthesia for laparoscopic surgery A.34
S. Odeberg, O. Ljungqvist, P. Gannedahl, T. Svenberg and A. Sollevi

Effects of plasma volume substitution on right ventricle volumes and function using Elohes® and Plasmion®........ A.35
J. Y. Lepage, F. Garrec, J. M. Malinovsky, A. Cozian and M. Pinaud

Alternating right to left ventricular ejection: the case of occult cardiac tamponade........ A.36
C. Skourtis, L. Karalazos and D. Setzis

Determinants of systolic pressure variation in patients ventilated after vascular surgery........ A.37
M. Beaussier, P. Coriat, M. Gosgnach, M. Portilla, P. Kalfon and P. Viars

15.40–17.10 Thursday 13 May, 1993—Astrid
Clinical circulation—General II (Oral session)

The systolic pressure variation predicts response to volume loading in patients ventilated after aortic surgery........ A.38
P. Coriat, C. Gomez, G. Daas, A. Perel and P. Viars

Influence of chronic angiotensin converting enzyme inhibition on systolic pressure variation during anesthetic induction........ A.39
L. Puybasset, B. Oris, P. Coriat, M. Gosgnach and P. Viars

Ketamine does not prevent hypotension caused by induction of anaesthesia with propofol in elderly patients........ A.40
D. Blockmans J. Van Hemelrijck and H. Van Aken

Effects of nitrous oxide (N_2O) on systemic haemodynamics, regional left ventricular (LV) function and incidence of myocardial ischaemia (MI) in vascular surgical patients with coronary artery disease (CAD)........ A.41
P. Hohner, C. Backman, G. Diamond, A. Friedman, S. Häggmark, G. Johansson, K. Karp and S. Reiz

Epidural clonidine and myocardial ischaemia after abdominal aortic surgery........ A.42
J. P. Fulgencio, J. M. Rimaniol, M. Saada, P. Catoire and F. Bonnet

Influence of positive pressure ventilation on myocardial ischaemia after abdominal aortic aneurysm repair........ A.43
D. McCoy, M. O'Connor, A. Cunningham and R. Dwyer

15.40–17.10 Friday 14 May, 1993—Lèopold II A
EXPERIMENTAL CIRCULATION (POSTER SESSION)

ABSTR. NO.

Functional recovery after 24 h preservation of rabbit hearts in University Wisconsin Solution.............................. A.44
J. L. Fellahi, F. Ouardali, S. Mouren, J.-F. Baron, M. Diaby and P. Viars

Effects of hypertonic saline on coronary blood flow and myocardial performance of a blood-perfused isolated rabbit heart... A.45
S. Delayance, G. Mion, S. Mouren, J.-F. Baron, M. Diaby and P. Viars

Pre- and intraoperative prevention by β-blockers, propranolol and esmolol, of ischaemia-induced ventricular fibrillation..... A.46
M. Freysz, Q. Timour, L. Bertrix, J. Loufoua and G. Faucon

Endocardial endothelium modulates in vivo left ventricular performance A.47
S. De Hert, T. C. Gillebert and D. L. Brutsaert

Does captopril modify the arterial response to vasopressor substances?.. A.48
E. Le Pelley, T. Chataigneau, J.-P. Richer, R. Tricoche and J. Fusciardi

Does exogenous dopamine reverse cardiovascular depression induced by isoflurane during thoracic epidural blockade?...... A.49
C. Raner, B. Biber, J. Lundberg, J. Martner and O. Winsö

Local versus neurogenic vasodilator effects of desflurane and isoflurane in the small intestine A.50
H. Sundeman, B. Biber, O. Winsö, J. Martner and C. Raner

A comparison between various hemodynamic parameters reflecting preload during graded hemorrhaege in ventilated dogs... A.51
S. Preisman, A. Shneider, U. Pfeiffer and A. Perel

Influence of cervicothoracic epidural anaesthesia (C-TEA) on left ventricular (LV) contractility – an experimental study in pigs with autonomous blockade A.52
S. Reiz, E. Nyström, M. Tugrul, S. Häggmark and G. Johansson

8.40–10.10 Wednesday 12 May, 1993—Dynastie A
RESPIRATION (ORAL SESSION)

Recruitment of atelectasis during general anaesthesia: a CT-study.. A.53
H. U. Rothen, B. Sporre, G. Engberg, G. Wegenius and G. Hedenstierna

The respiratory compliance in normal and obese subjects during anaesthesia A.54
D. Mulazzi, E. Calappi and M. Croci

Continuous spirometry: an aid in the intraoperative respiratory monitoring – case reports.................................. A.55
G. Bardoczky, E. Engelman and A. d'Hollander

Influence of posture on the respiratory mechanics during anesthesia.. A.56
E. Engelman, G. Bardoczky and A. d'Hollander

Continuous monitoring of the ventilatory mechanics during anaesthesia & intensive care.................................. A.57
C. Py, J. P. Perdrix, P. Baçonnier, A. Eberhard, J. M. Fargnoli, F. Coppo and V. Banssillon

Continuous monitoring of SpO2 during total intravenous anaesthesia with ketamine and spontaneous ventilation............ A.58
L.-M. Joly and D. Benhamou

15.40–17.10 Thursday 13 May, 1993—Lèopold II A
RESPIRATION (POSTER SESSION)

Hypoxic events after general anaesthesia in the recovery room.. A.59
D. Degasperi, M. Vinelli, C. Festa and M. T. Fiandri

Influence of anaesthesia on postoperative hypoxaemia.. A.60
L. Georgiou, A. Vourlioti, F. Kremastinou, P. Stefanou and A. Tsiotou

Early postperfusion assessment of gas exchange and postoperative extubation outcome following coronary artery surgery.... A.61
P. Knapik, J. B. Richardson and I. McLellan

Cerebral perfusion during obstructive sleep apnea (OSA) A.62
E. Bålfors and K. Franklin

Respiratory effects of laparoscopic cholecystectomy (preliminary data).. A.63
M. A. Crea, L. Sollazzi, V. Perilli, E. Marana and R. Ranieri

Abdominal wall retraction may decrease anaesthesiological risks of laparoscopic cholecystectomy......................... A.64
Z. Vereczkey, B. Babik, J. Fogas, J. Méray and B. Baltás

Diaphragmatic function after bupivacaine cervical extradural analgesia for chronic pain therapy......................... A.65
E. Nyström, E. Jansson, B.-I. Wenngren, R. Sharma, F. Clerque and S. Reiz

Direct, indirect or flexible laryngoscopy after thryoidectomy?... A.66
L. Lacoste, J. Karayan, M. S. Lehuedé, P. Ingrand and J. Fusciardi

Day 0 or day 3 laryngoscopy after thyroidectomy?.. A.67
L. Lacoste, J. Karayan, D. Thomas, T. Vallet and J. Fusciardi

Laryngeal function as assessed by tussometry following topical anaesthesia A.68
R. P. Mahajan, G. E. Murty, P. Singh and A. R. Aitkenhead

METABOLISM, NUTRITION, ENDOCRINOLOGY

8.40–10.10 Friday 14 May, 1993—Lèopold II A
Thermoregulation (Oral session)

ABSTR. NO.

Core-peripheral temperature difference in early vs later extubation after coronary artery surgery A.69
P. Knapik, J. B. Richardson and I. McLellan

Effectiveness of core warming on net transfer of body heat across the skin A.70
P. Kulkarni and F. Carli

Effect of premedication with nifedipine on intraoperative hypothermia A.71
N. Vassilieff, N. Rosencher, D. I. Sessler, C. Conseiller and A. Lienhart

Preoperative skin-surface warming reduces intraoperative hypothermia A.72
Y. Camus, E. Delva and A. Lienhart

An investigation into the effect of passive and active cutaneous warming devices on intraoperative body temperature in elderly patients A.73
J. Bennet, V. Ramachandra and F. Carli

Fentanyl, as pethidine, inhibits post anaesthesia shivering A.74
P. Alfonsi, J.-M. Hongnat, C. Lebrault and M. Chauvin

8.40–10.10 Friday 14 May, 1993—Astrid
Anaesthesia and transplantation I (Oral session)

Modification of the renin-aldosterone axis during orthotopic liver transplantation A.75
J. de los Ríos, M. J. Iribarren, P. Monedero, F. García-Pedrajas and J. L. Arroyo

Measurement of sigmoid intramural pH during orthotopic liver transplantation A.76
Y. Auroy, M.-C. Gillon, H. Bismuth and C. Ecoffey

Changes in blood lactate, total body oxygen delivery and consumption during liver transplantation A.77
J. Carrera, P. Monedero, M. J. Iribarren, J. de los Ríos and A. Panadero

Oxygen consumption is dependent upon oxygen delivery in cirrhotics undergoing liver transplantation A.78
P. Piccinni, A. Tripepi, L. Rossaro, F. De Zen and A. Pierri

Effects of desmopressin (DDAVP) supplementation in brain dead organ donors (BDOD) on early recipient renal function .. A.79
R. Guesde, S. Ourahma, B. Riou and P. Viars

Fiberoptic bronchoscopy in brain dead organ donors A.80
B. Riou, R. Guesde, Y. Jacquens, R. Duranteau and P. Viars

10.40–12.10 Friday 14 May, 1993—Astrid
Anaesthesia and transplantation II (Oral session)

Total intravenous anaesthesia (TIVA) with propofol and alfentanil for renal transplantation A.81
M. Kirvelä, A. Yli-Hankala and L. Lindgren

Prevention of acute tubular necrosis by volume loading in kidney transplantation A.82
C. Mouquet, J. Luciani, M.-O. Bitker and P. Viars

Volume loading and hormonal factors in the prevention of acute tubular necrosis in kidney transplantation A.83
C. Mouquet, A. Carayon, F. Clergue, J. Luciani, M. Bitker and P. Viars

Is the vasoconstrictive effect of cyclosporine mediated by endothelin in kidney transplantation? A.84
C. Mouquet, A. Carayon, S. Ourahma, M.-O. Bitker and P. Viars

Renal blood flow and function relationship in recent renal transplantation in man A.85
L. Jacob, J. J. Chazalet, D. Payen, J. Bedrossian, P. Teillac and B. Eurin

13.40–15.10 Friday 14 May, 1993—Lèopold II A
Metabolism—General I (Oral session)

Effect of recombinant human growth hormone (HGH) on protein metabolism in surgical patients A.86
F. Carli, J. Anderson, M. Read and D. Halliday

Glycine and its metabolites during and after intrauterine YAG laser surgery A.87
M. J. Van Boven, P. E. Pendeville and F. J. Singelyn

Carbohydrate deficient transferrin: A new copredictor of alcoholism related postoperative complications? A.88
T. Heil, C. Spies, T. Neumann and C. Müller

Effects of diazepam additives on the mononuclear phagocytic system A.89
J. C. Catalá, J. A. Carrera, M. J. Iribarren, F. García-Pedrajas and J. L. Arroyo

Adrenocortical function: A clinical comparison of Etomidat-Lipuro® and Hypnomidate® A.90
A. Wiebalck, B. Vanacker, H. Van Aken, L. Sermeus, R. Bouillon and A. Amery

Isoflurane inhibits Ca^{2+}-induced insulin secretion from electrically permeabilised islets of Langerhans A.91
J. P. Desborough, P. M. Jones, S. J. Persaud and S. L. Howell

15.40–17.10 Friday 14 May, 1993—Astrid
Metabolism—General II (Oral session)

Exercise and malignant hyperthermia: Family investigations A.92
G. K. Ribbens, L. Rodet, J. Borsarelli, M. Aubert and P. J. Cozzone

Is Burkitt's lymphoma an etiology or a differential diagnosis of malignant hyperthermia? A.93
A. Lienhart, H. Deriaz, H. Desnault, J. P. Masini and E. Delva

ABSTR. NO.

Inhibition of increase of blood thromboxane concentration by acetylsalicylic acid after release of tourniquet in lower extremity operations A.94
R. Ojanen, S. Kaukinen, E. Seppälä, L. Kaukinen and H. Vapaatalo

The combined prophylactic administration of H1 and H2 receptor blockers in the prevention of protamine related haemodynamic effects and the relation between antihistaminics – leucocytes and pulmonary vascular resistance A.95
P. Durak, A. Özgök, H. Esen, Ö. Erdemli and S. Ebil

The relationship between cardiopulmonary bypass related immunologic effects and complement, thromboxane and leucocyte parameters A.96
P. Durak, A. Özgök, G. Saydam, A. Türkmen, Ö. Erdemli and S. Ebil

15.40–17.10 Friday 14 May, 1993—Lèopold II B
Clinical circulation—Blood preservation (Poster session)

Use of aprotinin during cytoreductive surgery of ovarian cancer A.97
F. Lequeau, J. L. Bourgain, D. Castaigne and M. Samama

Blood requirements reduction in orthotopic liver transplantation with aprotinin A.98
P. Monedero, J. Carrera, J. Catalá, F. Carrascosa and J. L. Arroyo

High dose aprotinin versus desmo-pressin acetate treatment in cardiac surgery A.99
F. Hidalgo, J. A. Páramo, J. C. Catalá, F. Carrascosa and P. Monedero

Aprotinin does not decrease surgical bleeding and could promote arterial thrombosis in the pig: A prospective randomized, blinded study A.100
C. M. Samama, E. Mazoyer, P. Bruneval, P. Bonnin, M. Bonneau, G. Pignaud, P. Viars, J. P. Caen and L. O. Drouet

Effects of recombinant-human erythropoietin on postoperative transfusion requirements in subjects undergoing major orthopaedic surgery A.101
P. P. Faris, M. Ritter, R. Abels, D. Gordon and r-HuEPO Surgery Study Group

Peroperative autotransfusion in emergency surgery for spine trauma A.102
B. Riou, S. Cavallieri, R. Roy-Camille and P. Viars

Effects of postoperative autotransfusion in spine surgery A.103
B. Riou, M. Guerrero, M. Arock, M. Ramos and P. Viars

Acute preoperative plasmapheresis during cardiac surgery A.104
G. Armellin, D. Pittarello, D. Penzo and G. P. Giron

10.40–12.10 Wednesday 12 May, 1993—Dynastie A
NEUROSCIENCES (ORAL SESSION)

Transcranial Doppler sonography: effect of propofol and thiopental in patients with brain tumors and brain injuries A.105
W. Schregel, C. Geißler, U. Bredenkötter and H. Schäfermeyer

Jugular bulb metabolic monitoring during hyperventilation in severe head trauma patients A.106
C. De Deyne, T. Vandekerckhove, J. Decruyedaere, J. Poelaert and F. Colardyn

Sufentanil increases intracranial pressure in patients with head trauma A.107
J. Albanese, X. Viviand, O. Durbec, B. Alliez and C. Martin

Cardiac function in aneurysmal subarachnoid haemorrhage A.108
N. Moulay, V. Mahé, A. Descorps-Déclère, C. Cosson and C. Ecoffey

External ventricular CSF drains infections A.109
V. Mahé, N. Kermarrec and C. Ecoffey

EEG-monitoring during defibrillator-implantation: effects of repetitive cerebral ischemia on electric brain activity A.110
C. Spies, S. Kraemer, T. Heil, T. Neumann and K. Reinhart

15.40–17.10 Wednesday 12 May, 1993—Lèopold II A
NEUROSCIENCES (POSTER SESSION)

Midazolam prevents ketamine-induced stimulation of cerebral metabolism A.111
J. Åkeson, S. Björkman and K. Messeter

Nitrous oxide induced neuronal depression: modification through benzodiazepine receptors A.112
M. Dzoljic, E. Geller, J. Rupreht, W. Erdmann and M. R. Dzoljic

Dexmedetomidine does not exercise its anesthetic action through GABA A.113
M. Salonen, J. Kendig, B. O'Connor and M. Maze

Differential effects of specific delta and kappa opioid antagonists on the bidirectional effect of naloxone in arthritic rats A.114
I. Cattaneo, V. Kayser and G. Guilbaud

Effect of morphine on a nociceptive flexion reflex in patients with postoperative pain A.115
M. Chauvin, F. Guirimand, P. Gauneau and C. Lebrault

Involvement of μ, δ, and κ receptors in the inhibition by intrathecal morphine of a C-fibre evoked reflex in the rat A.116
F. Guirimand, M. Strimbu, J. C. Willer and D. Le Bars

Isoproterenol reverses the MAC decreasing effect of esmolol in rats A.117
A. Perel, A. Shneider and W. Kohn

Effect of esmolol versus lidocaine on intracranial pressure and haemodynamic responses to laryngoscopy and intubation A.118
T. Samaha, P. Ravussin, C. Clacquin and C. Ecoffey

ABSTR. NO.

Effects of intrathecal meperidine (MP) fentanyl (FN) and lidocaine (LD) on somatosensory (SSEP) and cortical motor (CMEP) evoked potentials in humans A.119
S. Fernandez, J. Monells, J. M. Espadaler and M. M. Puig

8.40–10.10 Thursday 13 May, 1993—Astrid
LOCAL AND REGIONAL ANAESTHESIA (ORAL SESSION)

Slow-release effect of pH-adjusted bupivacaine: Pharmacokinetic demonstration A.120
D. Benhamou, J.-M. Malinowsky, V. Quinquis, P. Bourget and G. Couarraze

Lemakalim reverses ventricular conduction impairment induced by a large dose of bupivacaine in anaesthetized dogs A.121
J. E. de La Coussaye, J. J. Eledjam, P. Bruelle, P. Peray and A. Sassine

Motor blockade and absence of local nerve toxicity induced by liposomal bupivacaine injected into the axillary brachial plexus of rabbits A.122
F. J. Legros, N. Lafont, M. Donnay and J. Boogaerts

The effects of bupivacaine, mepivacaine and prilocaine on platelet aggregation A.123
N. Bayhan, M. E. Güzeldemir and H. Türkan

The effects of epidural and spinal anesthesia on the changes in the plethysmographic signal in the lower and upper limbs ... A.124
S. Preisman, I. Eldar and A. Perel

The effect of parenteral diclofenac and morphine on efficacy duration and height of blockade during continuous epidural bupivacaine 0.5 % A.125
D. Forbes, A. Binning and N. B. Scott

10.40–12.25 Friday 14 May, 1993—Dynastie A
LOCAL AND REGIONAL ANAESTHESIA (ORAL SESSION)

Nine years of clinical experience with 29 gauge spinal needles A.126
M. Dittmann, H.-G. Schäfer, F. Renkl and I. Greve

Incidence of post dural puncture headache in young adults by the use of the Sprôtte needle: 300 patients A.127
C. Descraques, G. Mion, Y. Auroy, B. Lenoir, B. Pats, B. Rouvier and J. P. Chabanne

Postdural puncture headaches are not related to the duration of spinal catheter placement A.128
N. Liu, A. Montefiore, N. Kermarec, L. Beydon and F. Bonnet

Epidural blood patch for treatment of postdural puncture headache A.129
P. H. Rosenberg, T. Taivainen, M. Pitkänen and M. Tuominen

Sequential spinal peridural anaesthesia for gynaecological surgery under laparoscopy A.130
S. Joos, R. Quintilla and R. Servais

Subarachnoid anaesthesia (SAA) and post-operative analgesia with bupivacaine (BV) plus fentanyl (FN) in geriatric patients A.131
D. Fernandez C. Castells, M. Rue, M. Bernaus and M. M. Puig

Fentanyl or buprenorphine side effects in spinal anaesthesia A.132
R. Foppoli, P. Lunghi, Z. Bonara, C. Mora and R. Stacca

PHARMACOLOGY

8.40–10.10 Thursday 13 May, 1993—Dynastie A
Neuromuscular blockers I (Oral session)

Comparison between double-burst stimulation and 50, 100 Hz tetanic fade during spontaneous recovery of vecuronium induced neuromuscular blockade A.133
M. J. Baurain, B. S. Dernovoi, A. A. d'Hollander and D. M. Schmartz

Reversal of vecuronium induced neuromuscular blockade: No effects of atropine administration timing A.134
M. J. Baurain, B. S. Dernovoi, A. A. d'Hollander and P. C. Bollen

Can repetition of high frequencies stimuli alter the value of 50 and 100 Hz tetanic fade during vecuronium induced neuromuscular blockade? A.135
M. J. Baurain, B. S. Dernovoi, A. A. d'Hollander and D. M. Schmartz

Does nicardipine potentiate the neuromuscular block of atracurium? A.136
J. E. Bazin, T. Gillart, A. Comte, C. Dubray and P. Schoeffler

Neostigmine antagonism of neuromuscular blockade induced by mivacurium, vecuronium and atracurium A.137
B. S. Dernovoi, M. J. Baurain, A. A. d'Hollander and P. C. Bollen

13.40–15.10 Thursday 13 May, 1993—Lèopold II A & II B
Neuromuscular blockers II (Oral session)

The pharmacokinetics of rocuronium in pediatric patients: A pooled data analysis A.138
C. Meistelman, P. Fiset, B. O'Kelly, J. Frossard, B. Plaud and C. Ecoffey

Priming of atracurium with magnesium A.139
E. Lampl and M. Dandoy

Supra-additivity between atracurium and vecuronium A.140
O. A. Meretoja, B. W. Brandom, T. Taivainen and L. Jalkanen

Concentration-effect relationship at the vocal cords and the adductor pollicis following rocuronium administration A.141
B. Plaud, J. H. Proost, J. M. K. H. Wierda, B. Debaene, J. Barré and C. Meistelman

Monitoring the onset of neuromuscular blockade at the orbicularis oculi can predict good intubating conditions when using 2 × ED95 of atracurium A.142
B. Debaene, C. Meistelman, F. Donati and A. Lienhart

10.40–12.10 Wednesday 12 May, 1993—Lèopold II A
Pharmacology—General I (Poster session)

ABSTR. NO.

Preoperative clonidine improves postoperative renal function in CABG patients A.143
P. J. Kulka, M. Tryba, C. Menzel, F. Leurs and C. Frankenberg

Effects of oral preoperative guanfacine on anesthetic requirements A.144
E. Engelman and M. Lipszyc

Pharmacokinetics and effects of i.m. alfentanil as premedication for outpatient cataract surgery A.145
T. Ali-Melkkilä, M. Virkkilä, H. Soini and J. Kanto

Pharmacokinetic behaviour of transdermal fentanyl A.146
M. Van Bastelaere, G. Rolly and A. Van Peer

Sufentanil first-pass pulmonary uptake at three different steady state concentrations of the drug A.147
F. Boer, F. Engbers, T. Burm, J. Bovill and A. Hak

Computer-controlled syringe pump improves safety of pharmacokinetic models A.148
R. Duranteau, R. Guesde, B. Riou, H. Deriaz and P. Viars

Target-controlled intravenous sedation with propofol A.149
C. Mergaert, G. Rolly and L. Versichelen

Determination of a pharmacokinetic model for propofol induction of anaesthesia A.150
X. Viviand, C. Guidon-Attali, B. Lacarelle, C. Martin and G. François

10.40–12.10 Thursday 13 May, 1993—Lèopold II A
Pharmacology—General II (Poster session)

Pharmacokinetics of propofol and its conjugates after continuous infusion in normal and renal failure patients A.151
N. Nathan, J. Debord, F. Narcisse, J. L. Dupuis, G. Lachatre and P. Feiss

Propofol (2,6-diisopropylphenol) as an antioxidant in-vitro: A dose response study A.152
S. Bennett, V. Nelson and T. Green

Propofol anaesthesia with spontaneous breathing for extracorporeal shock wave lithotripsy A.153
T. Pasch and T. Hawelski

Quality of induction: A clinical comparison of Etomidat-Lipuro® and Hypnomidate® A.154
A. Wiebalck, B. Vanacker, H. Van Aken, L. Sermeus, R. Bouillon and A. Amery

Midazolam premedication: A forensic approach to pharmacokinetics and amnesia A.155
J. Motsch, S. Baller, A. Bach, R. Aderjan and E. Martin

Dose dependent effects of oral medication with midazolam A.156
P. Biro, E. Alon, G. Weidmann and S. Pietzsch

Flumazenil facilitates intraoperative arousal in scoliosis surgery A.157
Z. J. Koscielniak-Nielsen, J. Schierbeck, H. L. Stens Pedersen and G. Perko

8.40–10.10 Wednesday 12 May, 1993—Astrid
PAEDIATRIC ANAESTHESIA AND INTENSIVE CARE (ORAL SESSION)

Use of thoracic epidural block for perioperative analgesia in children A.158
A. H. Entress and S. P. S. Cheema

Blended anaesthesia in major paediatric surgery – Top-up vs continous epidural infusion A.159
G. Savoia, F. Lucke, G. Scermino, B. Sparacia and A. Sansone

Clonidine in paediatric caudal anaesthesia A.160
S. Jamali, S. Monin, C. Begon, A.-M. Dubousset and C. Ecoffey

Propofol for tracheal intubation in paediatric outpatient anaesthesia A.161
A. M. Montasser

Ventilation with halothane is less affected in children with laryngeal mask airway than with endotracheal tube A.162
J. Reignier, M. Ben Ameur and C. Ecoffey

Neuromuscular blockade following mivacurium in children during N_2O-halothane A.163
G. Orliaguet, B. Plaud, S. Calmatte and C. Ecoffey

10.40–12.10 Wednesday 12 May, 1993—Astrid
PAEDIATRIC ANAESTHESIA AND INTENSIVE CARE (ORAL SESSION)

Relationship between arterial PCO_2 ($PaCO_2$) and end tidal CO_2 ($ETCO_2$) recorded through a laryngeal mask (LMA) in children breathing spontaneously A.164
L. J. Van Obbergh, B. Zeippen, G. Muller and F. Veyckemans

Evaluation of the efficacy of forced-air warmer (Bair Hugger) during spinal surgery in children A.165
I. Murat, J. Bernière and I. Constant

Evaluation of a forced-air warmer (Bair-Hugger) in maintaining body temperature in infants during cleft palate surgery A.166
I. Murat, M. Delorme, V. Piat and M. C. Dubois

Comparison of dobutamine with enoximone following open heart surgery in small children A.167
P. Innes, E. Allsop, J. Lockie, C. Kirton and P. Booker

Extracorporeal membrane oxygenation for postoperative cardiac support in newborn infants: First clinical data A.168
A. Marcassa, C. Sorbara, G. Stellin, D. Pittarello and G. P. Giron

10.40–12.10 Wednesday 12 May, 1993—Lèopold II B
OBSTETRIC ANAESTHESIA (POSTER SESSION)

ABSTR. NO.

Diamorphine/bupivacaine mixture vs plain bupivacaine: A comparison of epidural infusions in labour ... A.169
C. R. Bailey, R. Ruggier and I. L. Findley

Patient controlled epidural analgesia vs. intermittent injections during labor using 0.125% bupivacaine and sufentanil ... A.170
J. Baudot, J. D. Vertommen and H. Van Aken

Adequate pain relief with epidural analgesia during labour: Why are women still dissatisfied? ... A.171
J. Hamza, P. Narchi, M. Elhaddoury and D. Benhamou

Spinal anesthesia for C section: Addition of phenylephrine to ephedrine for prevention of maternal hypotension ... A.172
A.-V. Thirion, M. Henry, A. Cornet, J. Seebacher and P. Viars

Headache – New needles and spinal anaesthesia for C. section ... A.173
F. Thormann, M. Henry, J. P. Soler, J. Seebacher and P. Viars

Best Quincke point needle for Caesarean section ... A.174
G. Lyons

Neonatal glycemia: Does the maternal iv fluid regimen during labour make a difference? ... A.175
C. Menigaux, J. Hamza, P. Bougnières and C. Saint-maurice

Epidural clonidine analgesia after major gynaecological surgery ... A.176
I. Smilov and B. Borissov

Mechanisms of ECG changes during Caesarean section (CS) – a hypothesis ... A.177
M. Svanström, G. Johansson and E. Bålfors

15.40–17.10 Thursday 13 May, 1993—Dynastie A
INTENSIVE CARE MEDICINE (ORAL SESSION)

Prolonged (> 1 week) sedation with midazolam in ICU patients: efficacy, safety and pharmacokinetics ... A.178
L. Heytens and L. Bossaert

Incidence of bacterial maxillary sinusitis in critically ill patients with radiologic maxillary sinusitis ... A.179
L. Bodin, P. Laurent, T. Do-Khac, A. Zouaoui, G. Lamas, E. Cambau, J. J. Rouby and P. Viars

Reassessment of bronchoalveolar lavage in the diagnosis of post traumatic pulmonary fat embolism ... A.180
O. Mimoz, A. Edouard, L. Beydon, F. Bonnet and K. Samii

Histology aspects of pulmonary barotrauma in critically ill patients with acute respiratory failure ... A.181
J. J. Rouby, T. Lherm, E. Martin de Lassale, P. Poete, L. Bodin and P. Viars

Comparison of pressure support ventilation provided by two ICU ventilators ... A.182
P. Kalfon, J. J. Rouby and P. Viars

Evaluation of cardiac function in ICU: Right heart catheterization *vs* transesophageal echocardiography. Preliminary results A.183
B. Vivien, E. Mourgeon, M. Saada, J.-P. Goarin, J.-J. Rouby and P. Viars

10.40–12.10 Friday 14 May, 1993—Lèopold II A
INTENSIVE CARE MEDICINE (POSTER SESSION)

Influence of norepinephrine therapy on the oxygen supply and lactate extraction rate of the liver in the septic pig ... A.184
R. Schäfer, W. Gerling, A. Utschakowski and K. Wagner

The effect of dobutamine and norepinephrine on global and splanchnic O_2 consumption ... A.185
A. Meier-Hellmann, L. Hannemann, D. Weyandt, W. Heiss-Dunlop and K. Reinhart

Influence of N-acetylcysteine on O_2 consumption and gastric intramucosal pH in septic patients ... A.186
C. Spies, I. Witt, C. Walensky, L. Hannemann and K. Reinhart

Molecular mediators and post-bacteraemic phase ... A.187
K. Martinez Urionabarrenetxea, J. L. Pérez Arancón, J. I. Yoldi, A. Camarero and J. L. Martínez

Molecular mediators and cardiac surgery ... A.188
J. L. Pérez Arancón, K. Martínez Urionabarrenetxea, J. I. Yoldi, A. Camarero and J. L. Martinez

Septic shock: Effect of a goal-directed therapy on oxygen metabolism and serum cytokine levels ... A.189
C. Martin, P. Saux, J.-L. Mege, G. Perrin and F. Gouin

Comparison of two therapeutic strategies of septic shock ... A.190
C. Martin, J.-P. Auffray, F. Potié and F. Gouin

Non invasive monitoring of CO_2 in patients with septic shock ... A.191
L. Bodin, H. Maghrebi, C. Kaddour, M. Arthaud, J. J. Rouby and P. Viars

13.40–15.10 Friday 14 May, 1993—Lèopold II B
RESUSCITATION AND EMERGENCY MEDICINE (ORAL SESSION)

Evaluation of systematic TEE in patients suspected of blunt chest trauma ... A.192
P. Catoire, L. Delaunay, L. Beydon, P. Guerrini and F. Bonnet

Diagnosis of aortic rupture by transesophageal echocardiography (TEE) ... A.193
J. P. Goarin, F. Le Bret, Y. Jacquens, B. Riou, M. Saada and P. Viars

Systemic gas embolism in pulmonary contusion diagnosed by transesophageal echocardiography ... A.194
M. Saada, B. Riou, J.-P. Goarin, J.-J. Rouby, Y. Jacquens and P. Viars

The choice of ECM rate could improve the neuroprotection during CPR ... A.195
E. Iannuzzi, E. De Blasio, F. Ferraro, A. De Sio and F. Schiraldi

ABSTR. NO.

Helicopter transportation of patients with symptomatic aortic aneurysms A.196
P. Felleiter, W. Breschinski and K. H. Bock

The part of rescue helicopters in large accidents and disasters A.197
O. Wenker

10.40–12.10 Thursday 13 May, 1993—Lèopold II B
ACUTE AND CHRONIC PAIN MANAGEMENT (POSTER SESSION)

Evaluation of pain and analgesia in a postanesthesia care unit A.198
F. Aubrun, P. Narchi and D. Benhamou

Organization of acute pain services – A low-cost model A.199
N. Rawal

Epidural administration of liposomal bupivacaine for the management of postsurgical pain A.200
J. Boogaerts, N. Lafont and F. J. Legros

Postoperative analgesia: A two dosage regimens trial for i.m. morphine after early i.v. titration A.201
K. Butscher J. X. Mazoit and K. Samii

Analgesia by wound infiltration before or after surgery in inguinal hernioraphy A.202
D. Hennart and Y. Mersch

Preemptive analgesia with epidural morphine A.203
I. Nègre, J. P. Guéneron, S. Jamali, S. Monin and C. Ecoffey

Addition of droperidol to PCA morphine: What is the optimal dose? A.204
C. T. Lamond, D. L. Robinson, J. T. Boyd and J. N. Cashman

Effects of epidural clonidine on anaesthetic requirements and postoperative analgesia A.205
E. Samsó, G. Murga, J. Valles, L. L. Gallart and M. M. Puig

15.40–17.10 Thursday 13 May, 1993—Lèopold II B
ACUTE AND CHRONIC PAIN MANAGEMENT (POSTER SESSION)

Safety of PCA in elderly A.206
E. Santangelo, B. Amantea, A. Sansone, G. Savoia and B. Sparacia

Postoperative hypoxaemia: Comparison of epidural and patient controlled analgesia A.207
A. Spencer, F. Farhat, J.-L. Bourgain and C. Jayr

Pharmacokinetics of intranasal fentanyl A.208
H. W. Striebel, J. Krämer, I. Luhmann, I. Rohierse-Hohler and A. Triltsch

Intranasal fentanyl for postoperative pain management in an unselected population A.209
W. H. Striebel, J. Pommerening, A. Rieger and G. Brummer

Intranasal fentanyl for breakthrough cancer pain or incident pain A.210
W. H. Striebel, A. Wessel, A. Rieger and N. Boerger

Treatment of cancer pain with morphine (MO) – A double blind study of extradural (ED) versus intramuscular (im) routes of administration A.211
S. Nath and G. Ehrenström Reiz

High dose oral morphine in cancer pain management A.212
L. Radbruch, S. Grond, D. Zech and K. A. Lehmann

Intrathecal pain relief in terminally ill cancer patients at home A.213
M. F. M. Wagemans, W. W. A. Zuurmond, E. M. Spoelder and J. J. de Lange

A.1

A NEW CLINICAL SCORE TO PREDICT DIFFCULT INTUBATION

Jean Arné, Pierre Descoins, Denis Bresard,
Jacques Ariès, Jacques Fusciardi

Department of Anaesthesia and Intensive Care,
University Hospital of Poitiers, Poitiers, France

Background and goal of study: The prediction of difficult intubation (DI) is very important in anaesthesia to reduce the morbidity related to failed intubation. The multifactorial index previously described [1-3] failed to predict DI in at least a quarter of the cases. The goal of this study was to test a new clinic score in an attempt to increase the sensitivity of prediction.

Materials and methods: 295 grown-up patients undergoing ETN or stomatological surgery were included in a prospective study. Our score was established by the assignment of points (0, 3, 5 or 7) depending on the degree of reach of seven factors : presence or not of a pathology known to be associated with DI, presence or not of clinic signs of airway's pathology, interincisive gap and mandible's luxation, thyro-mental distance, normal or short and broad neck, head and neck movement, and Mallampati's test. The intubation was defined as difficult when it required particular technics (special laryngoscope, fiberoptic intubation).

Results and discussion: The incidence of the DI was 8%; the best predicting level of the score has been determined at 11 using the "Receiver Operating Characteristic curves". A score higher than 11 foretells a DI with a sensitivity of 96%, a specificity of 90%, a positive predictive value of 46%, and a negative predictive value of 100%. The sensitivity of this score is better than with the multifactorial index of Wilson [1] (75%), Pottecher [2] (70%) and Frerk [3] (81%), with the same specificity. Moreover, these results are related to an ETN surgical population where the incidence of DI is higher than in general surgery : this fact induces a decrease in sensitivity of any test as compared to populations with a lower incidence of DI. Incidence of DI was lower in previous studies (1.5-6%) [1-3].

Conclusion: The sensitivity of the multifactorial clinic score seems to be improved when clinic signs of airway's pathology, and illness associated with DI are included. This conclusion remains true when a population with a high incidence of DI is concidered.

References:

[1] Wilson M, and al : British Journal of Anaesthesia 1988; 61 : 211-216.

[2] Pottecher T, and al : Annales Françaises d'Anesthésie et de Réanimation 1991; 10 : 430-435.

[3] Frerk C : Anaesthesia 1991; 46 : 1005-1008.

A.2

AN AUDIT OF THE INCIDENCE AND COSTS ASSOCIATED WITH POST OPERATIVE NAUSEA AND VOMITING (PONV) FOLLOWING MAJOR GYNAECOLOGICAL SURGERY IN AN INPATIENT POPULATION.

Morris RW[1], Ernst E, Greaves DJ, Layfield DJ,
Michael RF
[1]Princess of Wales Hospital, Bridgend, United Kingdom

118 inpatients, who had not received an anti-emetic in the 24 hours prior to major gynaecological surgery, were entered into a multicentre observational study to assess the incidence and costs associated with PONV. No restrictions were placed on the investigators' choice of anaesthetic agents.

For the first 24 hours after surgery detailed records of the incidence, frequency and resources used in treating PONV were collected by nurse observers not involved in caring for the patient. An emetic episode was defined as a single vomit or dry retch or any number of continuous vomits or retches. To count as a new episode, vomits or retches had to occur at least one minute after a preceding episode. Material costs were derived using mean cost data from all centres. National (UK) hourly rates for medical staff were used to value time spent treating patients and full NHS prices were used for anti-emetic drugs. These costs were used to estimate the mean cost of PONV per patient and the mean cost per emetic episode

Results: 45% of patients had an abdominal hysterectomy, 22% a laparotomy, 16% a vaginal hysterectomy and 17% some other major gynaecological surgery 40(34%) patients experienced PONV in the recovery room and spent a mean (S.D.) of 74.4 (35.9) minutes in recovery compared to 56.5 (26.4) minutes for patients not experiencing PONV in recovery ($p < 0.01$).

Over the full study period 98 (83%) patients experienced PONV and 75 (64%) had at least one emetic episode. The latter patients had a mean (S.D.) of 4.5 (3.6) emetic episodes per patient. Table 1 summarises the costs per patient of PONV and cost per emetic episode.

Table 1: Mean Cost of PONV per Patient

	N	Lab	Mat (£)	Drug (£)	Tot (£)
All Patients	117*	2.52	0.38	0.48	3.38
Patients with PONV	97	3.01	0.45	0.56	4.02
Patients with emesis	74	3.53	0.54	0.61	4.68
Cost per emetic episode		0.75	0.11	0.19	1.05

*One patient had emesis, but had missing resource data

Conclusion: This study suggests PONV frequently occurs after major gynaecological surgery giving rise not only to patient discomfort but also to additional NHS costs.

A.3

ANESTHESIA FOR PATIENTS ≥90 YEARS OF AGE IN EMERGENCY HIP SURGERY.

Eleftheriadis S.; Kuppe H.; Klotz K.-F.; Schmucker P.

Department of Anesthesiology, Medical University of Luebeck, Germany

INTRODUCTION: Persons ≥ 90 years of age represent a rapidly growing segment of our population. Progress in surgery, anesthesia and the more liberal use of perioperative invasive monitoring increases the surgical rates in these patients (1).

PATIENTS AND METHODS: In an 18 months period, 37 Patients (34 women) ≥ 90 years of age underwent surgical correction of a fractured neck of femur. Preoperative risk factors included: Hypertension (54%), cardiovascular (67%), respiratory (43%) and cerebrovascular disease (32%). Prior to induction of anesthesia a radial arterial and a jugular vein catheter were inserted; in 12 patients a pulmonary arterial catheter too. Thirty-one patients received a spinal and six patients general anesthesia.

RESULTS: The baseline cardiac output (CO) was 4,9±1,2 l/min.. Through subtle volume loading and vasoactive drugs the CO and the arterial blood pressure were maintained stable throughout the operation. The mean blood transfusion was 535 ml/patient. Due to increased O_2-Consumption, O_2-insufflation was necessary in the immediate postoperative period. Hospital deaths were 5 (13,5%).

CONCLUSIONS: The ≥ 90 years aged, with his limited reserves, requires our intensive interdisciplinary attention. The exact preoperative evaluation of the patient, precise intraoperative monitoring, maintenance of hemodynamic stability and normoxaemia as well as optimal postoperative care, are the important prerequisites for successful handling.

1.Warner MA, Hosking MP, Lobdell CM, Offord KP, Melton LJ: Surgical procedures among those ≥90 years of age: A population based study in Olmsted Country,Minnesota,1975-1985.
Ann. Surg. 207:26-32,1988.

A.4

A SURVEY OF SLEEP PROBLEMS IN SURGICAL PATIENTS.

L. Beydon, A. Rauss, F. Lofaso,
A. Harf, F. Bonnet.

Dept of Anesthesia. Henri Mondor Hospital,
94010 Créteil - France.

Insomnia is a common complain in surgical patients. In order to appreciate its prevalence and promoting factors we conducted a questionnaire survey in 176 consecutive patients who had elective surgery, in three surgical departments (general, orthopedic, vascular). Three questionnaires were filled out: 1) the day before surgery, 2) the day of discharge, 3) 15 days after discharge. They included 58 questions about subject personality, usual and postoperative sleep profile and sleep quality, intensity of hospital disturbances and pain, physical fitness, previous surgical experience. Answers were given in a quantitative form. 89.2 % of patients (52.3 men, 51.9 ± years, 80 % ASA I-II, hospital stay: 9.9 ± days) completed the whole study. 42 % received hypnotic drugs the night before surgery, 35.2 % were hospitalized in single room, 16 % stayed in ICU postoperatively, 42 % of patients needed more than 4 days to recover sleep, postoperatively. Complain about night cares and noise were noted in 23 and 17 %. Sleeping pills were taken by 18, 38, and 27 % of patients, in day life, after surgery and 15 days after discharge (D_{15}) respectively. Pain at D_{15} was noted in 47 % and requiring analgesics in 33 %. Factor analysis showed that self-rated postoperative insomnia was related to three major variables: pain (p=0.0002), a poor sleeper profile in day life (p=0.003) and the level of anxiety facing surgery (p=0.04). Environmental disturbance, psychological profile, previous surgical experience did not participate to the level of postoperative insomnia. Those who experienced poor postoperative sleep were those who still did not sleep well, 15 days after discharge. In conclusion, the complain of poor sleep in the early postoperative period is frequent. Pain represents one major etiologic factor for insomnia. Improving analgesic therapy probably could improve sleep and comfort at night in the early postoperative period.

A.5

INDICATIONS FOR CORONARY REVASCULARISATION IN VASCULAR SURGICAL PATIENTS.

Marilyn Gosgnach, Pierre Coriat,
Marie-Hélène Fleron, Michèle Bertrand, Pierre Viars.
Department of Anesthesiology, CHU Pitié-Salpêtrière,
University Paris VI, Paris, France.

Background: In patients undergoing vascular surgery preoperative coronary angioplasty (PTCA) or bypass graft surgery (CABG) might reduce the perioperative risk and more importantly improve the long term survival of these high risk individuals (1). Accordingly, one of the main goal of the preoperative assessment is to identify the patients in whom a coronary intervention is needed prior to surgery. The aim of this study is to compare the percentage of indications for coronary intervention in patients undergoing surgery for occlusive disease of the abdominal aorta (O.D.A.) vs abdominal aortic aneurysm (A.A.A.) vs carotid endarterectomy (C.E.).

Methods: All patients, aged between 55-71 years, admitted to our institution during 1992 for abdominal aortic or carotid surgery were included in this study. A routine coronary angiography was performed as part of the preoperative assessment in these 127 consecutive patients.

Results: The prevalence and the severity of coronary artery stenoses are shown in the table according to the type of the vascular disease.

	O.D.A.	**A.A.A.**	**C.E.**
n	40	41	46
Mean age	62 yrs	65 yrs	63 yrs
Clinical CAD	n = 10	n = 13	n = 14
At least one coronary artery stenosis			
> 50 %	n = 21	n = 30	n = 32
> 70 %	n = 11	n = 28*	n = 22*
Coronary steal prone anatomy			
n	n = 3	n = 5	n = 6
indication for myocardial revascularisation			
n	n = 1	n = 11*	n = 11*
PTCA/CABG	1/0	7/4	2/9

* $p < 0.005$ vs 0.D.A.

Conclusion: Coronary revascularisation was indicated in one quarter of patients scheduled for A.A.A. or C.E., but only in 3 % of patients with O.D.A.. This should be taken into account for the preoperative management of these patients.

References: (1) Reul G. et al : The effect of coronary bypass on the outcome of peripheral vascular operations in 1093 patients. J. Vasc. Surg., 3 : 788-798, 1986.

A.6

DOES ROUTINE PREOPERATIVE CORONARY ANGIOGRAPHY MODIFY OUTCOME AFTER AORTIC SURGERY ?

Marilyn Gosgnach,Michèle Bertrand, André Pironkov,
Pierre Coriat ,Pierre Viars
Department of Anesthesiology, CHU Pitié-Salpêtrière,
University Paris VI, Paris,France

Background and goal of the study: Early studies in vascular surgical patients with CAD identified by coronary arteriography (CA), suggested that coronary intervention (PTCA or CABG) could reduce cardiac morbidity following aortic surgery (1). The aim of this study was to determine whether this approach actually decreases the risk for perioperative coronary complications: myocardial ischemia or infarction (MI).

Material and methods: 111 Consecutive (61-70 year old) patients scheduled for aortic surgery were prospectively studied a comparison between the incidence of postoperative cardiac complications in patients admitted during the year 1990 (group 1) who had only a standard clinical preoperative work up and in patients admitted during 1991 in whom a CA was part of their routine preoperative evaluation (group 2) was made.

Results:

	group 1 : 1990	group2 : 1991
n	57	54
PTCA	0	7 (6 successful)
CABG	0	7
perioperative ischemia	14/57	12/51*
postoperative MI	1	1

* aortic surgery was not performed in 2 patients who underwent CABG and in one patient who died before the coronary intervention.

Conclusion: Routine preoperative CA did not lead to an increased mortality or morbidity. Although routine preoperative CA resulted in performing coronary intervention in 14 % of the patients, this invasive preoperative screening test did not reduce cardiac morbidity following the subsequent aortic surgical procedure. Further studies are needed to determine whether this approach improves long term survival of these high risk individuals.

Reference: Acinapura A.J. et al : Role of coronary angiography and coronary bypass surgery prior to abdominal aortic aneurysnectomy. J. Cardiovasc. Surg.,128:552-557, 1987

A.7

OUTCOME FOR PATIENTS IN INTENSIVE CARE WITH ACUTE RENAL FAILURE REQUIRING DIALYSIS

Ellen Ejlersen, Maiken Brit Jensen, Kirsten Eliasen,

Departments of Anaesthesia and Nephrology, Herlev Hospital, University of Copenhagen, Denmark

Background and goal of study: Acute renal failure (ARF) carries a high mortality. Most reports cite the mortality to be in the range 50-90%. Despite improvement in the management of critically ill patients the mortality has failed to improve through the last 20-30 years. The purpose of our study was to review the experience of ARF treated in a single ICU, to evaluate if mortality has changed from early to late period of study, and to identify factors which might have influenced outcome.

Materials and methods: All ICU patients with ARF needing dialysis in the period 1977-1989 were included. The study was retrospective.

Results and discussion: Of the 167 patients included, 129 were men and 38 women, median age was 60 y (range 14-82). 58% developed ARF complicating surgery. 42 patients (25%) survived, two of whom continued chronic dialysis treatment. Age above 60 y ($p<0.02$), requirement of mechanical ventilation ($p<0.0005$), administration of inotropic drugs ($p<0.0005$), and increased serum bilirubin levels ($p<0.005$) had negative influence on survival. Mortality increased significantly from 63% during the early period (1977-85) to 84% during the late period (1986-89), probably due to selection bias with a more morbid population being treated in the later years.

Conclusion: One quarter of ICU patients with ARF requiring dialysis survived. Of the proportion of patients requiring mechanical ventilation only 20% survived. The survival rate was further reduced to 11% for patients who developed jaundice and required vasopressor therapy in addition to mechanical ventilation.

Reference: Wheeler DC, et al: High risk acute renal failure. QJ Med 1986; 61:977-84.

A.8

A NATIONAL DATABASE FOR INTENSIVE CARE MEDICINE IN SWEDEN.

Mats Karling

Department of Anaesthesia and Intensive Care Medicine, University of Umeå, Umeå, Sweden.

Background: Intensive care is an expensive area of medical care which is associated with high mortality. In the United States (US) the cost of intensive care is estimated to be around 1% of GNP. In Sweden the cost is around one half of that in the US. Mortality is about 20% in the intensive care unit (ICU) and around 30% at one year. Validated methods for outcome prediction and quantitation of care exist (1, 2). These can be used to compare the results and costs from different centres (3). This paper describes the Swedish national data base system for intensive care which will be operational from Jan. 1st 1993.

Patients and methods: Data from all patients admitted to a member ICU, with the exception of those with uncomplicated postoperative course, are collected in a local database. The following variables are registered; *First 24 hours:* APACHE II, route of admission, demographic data. *Daily:* TISS, major therapeutic interventions and number of ICU staff for each shift. *At discharge:* patient's status and diagnoses. The contents of the local database are sent to a central database every three months. This database retrieves deaths from the Swedish Population Register (SPAR) every six months. Each participating centre receives a report comparing their mortality ratio according to APACHE II predicted outcome, with the average ratio and the ratio within the same type of unit.

Discussion: At present, 60 of 96 ICU-s participate. This includes all major hospitals in Sweden. The database will make it possible to get an overview of ICU use in Sweden. APACHE II will be a tool for the comparison of results and a standard for quality assurance. The resources needed to obtain these results will be measured from TISS and ICU staffing. The value of certain expensive therapeutics such as ECMO, plasmapheresis and haemodialysis, can be analysed. It is estimated that the size of this database will allow detection of changes in medical practice.

References: (1) Cullen et al: Crit Care Med 1983, 11:13, (2) Knaus et al: Crit Care Med 1985, 13:10. (3) Knaus et al: Ann Int Med 1986;104.

A.9

A COMPARAISON OF MIDAZOLAM AND MIDAZOLAM PLUS FENTANYL FOR COLONOSCOPY.

Hervé Dupont, Jean-Baptiste Nyarwaya, Kamran Samii

Département d'Anesthésie-Réanimation
Université Paris Sud,Hôpital de Bicêtre
94275 Le Kremlin-Bicêtre cedex
France

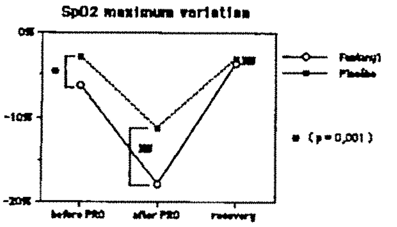
***Background and goal of study*:** Colonoscopy (C) is a painful procedure usually performed with sedative drugs (1). The addition of opioids to sedative drugs may increase the tolerance of the procedure (2) but increases the risk of respiratory depression (3). The purpose of this prospective, double blind, randomized study was to evaluate the benefit and risk of the addition of fentanyl (F) to midazolam (M) during Colonoscopy.

Materials and methods: After ethical approval, sixty patients, ASA 1 to 3, were randomized to receive M+placebo (MP group) or M+F (MF group). Mean arterial blood pressure (MAP), heart rate (HR), respiratory frequency (RF) and pulse oxymetry (SpO$_2$) were monitored every 10 min during C and in the recovery room during 90 min. Sedation score (S) from 0 to 4 and endoscopy conditions score (EC) from 0 to 2 were evaluated. Sedation was induced with M=2mg and F=1µg/kg. Additional boluses of M=1mg were injected with a 5 mg limit total dose in order to reach an EC score of 2. In case of failure, another F=1µg/kg was given. Finally, Propofol (P) was used (up to 1mg/kg), to reach an EC score of 2. If SpO$_2$ < 90%, RF < 12/min or S score of 4 were observed, 3L. mn^{-1} O_2 was administered under spontaneous or assisted ventilation. Statistical analysis included ANOVA for quantitative data and Chi-Squares test with Yates' correction for categorial data.

Results and discussion: Both groups were comparable except for age (57.8±15.7 yr vs 47.6± 13.9 yr, p=0.01) and MAP (110±18 mmHg vs 100± 14 mmHg, p=0.02) for MP and MF group respectively. There was no difference in S scores between groups, but EC scores were higher in MF group (p=0.01). In the recovery room, abdominal pain was lesser in MF group (p=0.02). In the MP group, it was necessary to use more M (p=0.02), P more often (p=0.03) and to higher doses (p=0.04). The frequence of a deacrease in SpO$_2$ >5%, the lower value of SpO$_2$ and the maximum deacrease variation in SpO$_2$ were significantly different between MF and MP group (69 vs 31%,p=0.03, 92±5% vs 95±3%,p=0.01, -6±5% vs -3±2%,p=0.001). After P, apneas were more frequent in MF group (p=0.01).

Conclusion: We conclude that the addition of F to M entails better EC score, less P general anesthesia, less abdominal pain but an increased respiratory depression.

References: (1) Gastroenterol Clin Biol 1989; 13: 651-653 /(2) Br J Anesthesia 1984; 56: 1109-1111 /(3) Acta Anesthesiol Scand1991;35 : 767-770



A.10

EVALUATION OF SACCADIC EYE MOVEMENTS AS AN OBJECTIVE TEST DURING RECOVERY FROM ANESTHESIA

Olivier Paut, Jean Louis Vercher, Olivier Blin, Daniel Mestre, Jean Camboulives

Department of pediatric anesthesiology and intensive care, La Timone University Hospital, Marseille, France

Background and goal of the study: Saccadic eye movements have been used to assess residual effects of anesthetics (1), but there is no data concerning comparison of this assessment method with other psychomotor tests during recovery from anesthesia. The aim of this study was to evaluate saccadic eye movements measurement as an objective test of recovery from anaesthesia, in comparison with subjective and objective tests of reference.

Material and methods: This randomized, double blind, crossed over, placebo controlled study was approved by the University ethical commitee. After informed consent given, 8 healthy, male volunteers, aged 25 years, weighting 76 kg were included. They received 0.15 mg.kg^{-1} IM of midazolam (MDZ) or placebo (PLA) during two experimental sessions separated with at least one week of interval. Psychomotor function was assessed before induction (t0) and 30 (t30), 60 (t60), 120 (t120), 180 (t180), 240 minutes after injection (t240), using a battery of tests including: Visual analogic scales (VAS), Choice reaction timer (CRT) and saccadic eye movements (SEM) measurements with electrooculogram detection, allowing registration of SEM parameters [ie latency, peak saccadic velocity (PSV), duration]. Blood samples were obtained at the same study time in order to determine plasma concentrations of MDZ. Statistical analysis was made using one way ANOVA for repeated measures and Dunnett's test.

Results and discussion: Main results are shown in table I. In the PLA group, there is no difference between each study evaluation concerning saccadic parameters and VAS. On the other hand, there is a significant difference during time concerning CRT, with a decrease of performance from t60 to t180 (ANOVA p < 0.01, Dunnett's test p < 0.05). In the MDZ group, there is a significant difference for CRT from t30 to t180. Saccadic parameters are significantly different from t30 to t120 (latency, duration) and from t30 to t180 for PSV (ANOVA p < 0.0001, Dunnett's test p < 0.05).

VAS assessment showed that only 5 items were significantly different from t30 to t120 (drowsy, on form, tired) at t60 and t120 (clumsy) or only at t120 (woolly).

Conclusion: These results show that SEM measurement is a good tool for assessing residual effects of anesthetics during recovery from anesthesia. We found this test more reliable and robust than CRT, chosen as a test of reference. Saccadic eye movements are altered by MDZ used with premedicant doses, and a 3 hours delay is needed for a complete psychomotor recovery. Subjective assessment using VAS is not a reliable method, subjects tending to underestimate their status in the early study period, in the MDZ experimental session.

Table I: Time course of psychomotor performance in the placebo group (PLA) and midazolam group (MDZ). *p<0.05 (Dunnett's test, after ANOVA).

		t0	t30	t60	t120	t180	t240
CRT	MDZ	32,9	90,9*	70,3*	51,7*	42,9*	36,2
10^{-2}s	PLA	33,7	34,8	35,8*	37,7*	36,1*	35,2
PSV	MDZ	301,3	160,4*	180,3*	237,7*	266,5*	293,8
	PLA	301,8	297	300,6	290,1	296,9	292,5
Latency	MDZ	173	286,2*	264*	206*	184,1	178,7
	PLA	166,3	167,2	167,6	169	167,5	168
Duration	MDZ	2,54	6,51*	5,48*	3,69*	3,1	2,59
	PLA	2,48	2,5	2,53	2,59	2,5	2,61
[C]µg/ml]	MDZ	0	177	144	93	67	47

Reference: (1) Gao F at al. Effect of low concentrations of nitrous oxide and isoflurane on peak velocity of saccadic eye movements. Br.J.Anaesth. 1991, 66: 179-184.

A.11

ALIZAPRIDE DOES REDUCE PAIN ON INJECTION OF PROPOFOL : COMPARISON WITH LIDOCAINE.

ZAOUK G., M.D., GILBART E., M.D., DUBOIS A., M.D., JACOBS D., M.D., BALATONI E., M.D.

University Hospital Center A.VESALE,
MONTIGNY-LE-TILLEUL - BELGIUM.

Background and goals of the study: Propofol (P) is an intravenous hypnotic drug with many suitable characteristics. Pain due to its injection is a well recognized problem. Lidocaine (L) has been used with efficacy to reduce the incidence of pain on injection of P (1). Alizapride (A) is a benzamide derivative structurally related to procainamide known to be an effective anti-emetic drug in cytotoxic- and anesthetic-induced vomiting. The purpose of this study was to evaluate the efficacy of A compared with L in reducing pain on injection of P.

Materials and methods: After approval by local Ethics Committee, we studied 300 patients (ASA 1-2) scheduled for various elective surgical procedures. Subjects were allocated randomly to 3 groups (N=100) and received, on a double-blind basis, either 1 ml 0.9% NaCl or 1 ml 1% L or 1 ml A (25 mg) immediately before injection of P. The pain score used was : 0 = no pain even on demand; 1 = complaint of pain when asked after 50% of the total dose; 2 = spontaneous complaint before 50% of the total dose; 3 = pain with arm retraction, grimacing or both.

Results: The 3 groups were comparable in their sex, age, weight and ASA distribution (ANOVA, Chi-squared and Fischer tests). Both L and A significantly reduced pain on injection of P when compared with saline, but L reduced it more than A (Table 1).

TABLE 1

score :	0	1	2	3
NaCl :	22	17	20	41
A :	44	34	12	10
L :	82	16	0	2

Overall Kruskall-Wallis test : p=0.0001
Wilcoxon rank sum test for individual
comparisons : p=0.0001 NaCl vs L
p=0.0001 NaCl vs A
p=0.0001 A vs L

Discussion: In conclusion, A can be an useful alternative for reducing pain on injection of P in short surgical procedures, especially when antiemetic properties are needed, as in outpatient anesthesia.

References:

1.Gehan G. et al : Optimal dose of lignocaine for preventing pain on injection of propofol. Brit J Anaesth 1991; 66: 324-6.

A.12

ONDANSETRON 4 mg VS DROPERIDOL 1.25 mg IN THE PROPHYLAXIS OF POSTOPERATIVE NAUSEA AND VOMITING AFTER ALFENTANIL-SUPPLEMENTED INHALATION ANAESTHESIA

Eli Alon, Philipp M. Lenzlinger, and Thomas Pasch

Department of Anaesthesiology, University Hospital, Zurich, Switzerland

Introduction: Ondansetron, a selective 5-HT_3 receptor antagonist, has recently been shown, in a dose of 8 mg, to be superior to droperidol 1.25 mg in preventing postoperative vomiting (1). There are indications that a dose of 4 mg of ondansetron may be just as effective in reducing postoperative nausea and vomiting as a dose of 8 mg (2). The aim of this study was to evaluate the efficacy and the adverse effects of 4 mg ondansetron in the prevention of postoperative nausea and vomiting compared to droperidol in patients undergoing surgery with inhalation anaesthesia supplemented with alfentanil.

Methods: Following institutional approval, 40 ASA physical status I and II women scheduled for minor gynecological surgery gave informed consent to participate in this randomized, double-blind comparative study. Five minutes before induction of general anesthesia, 20 patients received a single intravenous (IV) dose of 4 mg of ondansetron and the remaining 20 received 1.25 mg droperidol IV. Anesthesia was induced with 2.1 - 4 mg/kg of thiopental and 0.1 mg of alfentanil IV and maintained with 65% nitrous oxide and 1.5%-3% enflurane in oxygen. On pain stimuli another 0.2 - 0.4 mg of alfentanil were given. Total effective antiemetic response was defined as the absence of nausea and vomiting for 24 hours postoperatively. The incidence of nausea, vomiting and the number of patients showing total antiemetic response as well as the incidence of adverse effects were compared with the chi^2 - test and $p < 0.05$ was considered significant.

Results: Patients were similar with respect to age, height, body weight and total anaesthetic agents received. Duration of anaesthesia and the time for awakening was not significantly different among the groups. Postoperatively 7 out of 20 patients (35%) given 4 mg of ondansetron and 3 out of 20 patients (15%) with droperidol vomited (statistically not significant). The incidence of nausea was 55% (11/20) in the ondansetron group, and 20% (4/20) in the droperidol group ($p < 0.05$). 16 patients (80%) in the droperidol group and 8 patients (40%) in the ondansetron group showed a total effective antiemetic response ($p < 0.05$). Postoperative sedation and well-being scores did not differ significantly among the groups.

Discussion: A recent study (1) showed that ondansetron in a dose of 8 mg given preoperatively was superior to 1.25 mg droperidol in reducing postoperative vomiting. Our results show that 4 mg ondansetron was inferior to 1.25 mg droperidol given preoperatively in reducing nausea and vomiting after alfentanil-supplemented general anesthesia for minor gynecological surgery.

References: 1. Anesth Analg 1992;75:561-5
2. Anesthesiology 1992;77:A18

A.13

DOUBLE-BLIND COMPARISON OF ONDANSETRON, DROPERIDOL AND SALINE FOR PREVENTION OF NAUSEA & VOMITING AFTER ORTHOPAEDIC SURGERY

TJ Gan, R Collis, M Hetreed

Department of Anaesthesia, Royal National
Orthopaedic Hospital, Stanmore, Middlesex, UK

Background and goal of study: The incidence of postoperative nausea and vomiting (PONV) is as high as 83% after major orthopaedic surgery.[1] Ondansetron (O), a selective 5HT-3 antagonist, is suggested to be superior to other antiemetics in preventing PONV. This study compared its efficacy against droperidol (D) and saline (S) in patients after orthopaedic surgery.

Materials & methods: 93 ASA 1 & 2 patients undergoing hip or knee replacements, or femoral resections, received a standardised, combined epidural (10 ml 0.5% plain bupivacaine) and general (20 mg temazepam premedication, 2.5 mg/kg propofol induction, 66% nitrous oxide in oxygen, 2% enflurane, breathing via laryngeal mask) anaesthesia. At the end of surgery they were blindly randomised to receive either 1.25 mg D, 4 mg O or 0.9% saline. These were given intravenously over 10 mins in a 25 ml bag previously prepared by the pharmacy department. A Nausea and Vomiting chart was recorded by the nursing staff hourly for 24 hours. Side effects and administration of rescue antiemetic (10mg metoclopramide) were also recorded.

Results:

	n	no symptoms (%)	nausea (%)	vomiting (%)
O	33	21 (64)	7 (21)	5 (15)
D	28	17 (61)	7 (25)	4 (14)
S	32	9 (28)	8 (25)	15 (47)

Length of operation, weight, age and gender were similar between groups. Both O & D were superior to S in preventing PONV ($p<0.01$) though no significant difference was seen between them. However, metoclopramide was demanded by 34%, 29% and 9% of S, D and O patients respectively (D vs O $p<0.05$). Side effects from O & D were minimal.

Conclusion: Although O & D were equally effective in suppressing PONV, the reduced requirement for metoclopramide suggests that O provides greater subjective benefit.

References:

[1] Statistical Bulletin. Dept of Health HMSO 2(1)92

A.14

COMPARISON OF ONDANSETRON, METOCLOPRAMIDE AND DROPERIDOL FOR THE PROPHYLAXIS OF EMETIC SYMPTOMS AFTER GYNECOLOGICAL LAPAROSCOPIC PROCEDURES

Christine Geiger, Ottmar Kick, Hubert Böhrer, Johann Motsch
Eike Martin
Department of Anesthesiology,
University of Heidelberg, Heidelberg, Germany

Background and goal of study: Nausea and vomiting is a common problem after gynecological laparoscopic procedures. We evaluated the prophylactic efficacy of ondansetron, a selective 5-HT_3 antagonist in comparison to metoclopramide and droperidol.

Materials and methods: 60 ASA 1 patients, scheduled for gynecological laparoscopic procedures were randomly assigned in a double blind manner to receive either 8 mg ondansetron, 10 mg metoclopramide or 1.25 mg droperidol 2 min prior to induction. All patients were premedicated with 7.5 mg midazolam orally 45 min prior to induction. Anesthesia was induced with propofol 2.0-2.5 mg/kg, fentanyl 0.1 mg, succinylcholine 1 mg/kg and vecuronium 0.6 mg/kg. Anesthesia was maintained with 70% nitrous oxide in oxygen and isoflurane. An orogastric tube was placed after intubation and removed prior to extubation.The patients were followed up for emetic symptoms for 24 hrs. Data were analyzed using Chi-square tests, with $p < 0.05$ considered statistically significant.

Results and discussion: Patient characteristics and main results are listed in the table.

Parameter	Ondansetron	Metoclopramide	Droperidol
Number of patients	20	20	20
Age (yrs)	32±9	29±6	35±9
Duration of surgery (min)	30±21	31±25	21±11
Duration of anesthesia (min)	59±21	59±25	49±14*
Nausea (n)	1	3	2
Vomiting (n)	0	2	3

* = $p < 0.05$

Our anesthetic technique, which is considered to be associated with relatively few emetic sequelae, led to a low incidence of postoperative nausea and vomiting in all of the three study groups. The absence of vomiting with ondansetron was not statistically different in comparison to metoclopramide or droperidol.

The duration of operation, significantly shorter in the group treated with droperidol, did not show any correlation with the incidence of postoperative nausea and vomiting. Three of the patients treated with ondansetron spontaneously reported about an astonishing well-being after recovering from anesthesia.

Conclusion: We conclude that ondansetron given prophylactically prior to induction of anesthesia is a potent antiemetic agent without major side effects. It may not be superior to metoclopramide or droperidol in the prevention of vomiting after gynecological laparoscopic procedures.The euphorising effect of ondansetron seen in some patients needs further investigation.

Reference: Anesth Analg; 1992 75: 561-565 .

A.15

CLINICAL EVALUATION OF THE CALIBRATION OF NONINVASIVE CONTINUOUS BLOOD PRESSURE MEASUREMENT DEVICES BY MEANS OF OSCILLOMETRIC BLOOD PRESSURE MEASUREMENTS.

Jan R. de Jong, Henk H. Ros, Jaap J. de Lange

Department of Anaesthesiology, Free University Amsterdam, the Netherlands

Background and goal of study: in recent years three types of non- invasive (semi-) continuous blood pressure measurement devices have entered the market. The Finapres, which uses a volume clamp technique, the Cortronic, which uses brachial artery pulsations, and the N-Cat which uses radial artery tonometry to determine the blood pressure. The latter two devices use oscillometrically determined blood pressure measurements from the upper arm to calibrate their continuous blood pressure measurements. The goal of our study was to determine whether oscillometric blood pressure measurement is an appropriate technique for calibration of noninvasive continuous blood pressure measurement devices.

Materials and Methods: in 11 patients (5 with Cortronic and 6 with N-Cat) Noninvasive blood pressure was measured on one arm, intra arterial blood pressure on the other arm. After each calibration sequence the first calibrated noninvasive analog waveform was recalibrated against the corresponding intra arterial waveform. For each recalibration this resulted in a multiplication factor (m.f.) for correction of differences between the systolic - diastolic amplitudes, and in a constant for bringing the two waveforms up to the same level. In both the Cortronic and the N-CAT group the median and the 2.5th and 97.5th percentile limits of agreement (1) were determined for the multiplication factor and for the constant. Also the correlation coefficient of the multiplication factor and the constant was determined.

Results and discussion: in the Cortronic group 154 calibrations were analyzed, the median and limits of agreement for the multiplication factor were: 1.04, 0.43 and 1.42 and for the constant: -10.7, -69.3 and 36.8 mm Hg. The correlation coefficient was R = 0.91. In the N-CAT group 93 calibrations were analyzed, the median and limits of agreement for the multiplication factor were: 0.72, 0.37 and 1.37 and for the constant: 20.1, -31.4 and 39.2 mm Hg. The correlation coefficient was R = 0.87. Our method of analyzing the calibration measurements is new and it provides a quantitative description of the effect a calibration mismatch will have on the subsequent continuous measurements in the event of blood pressure changes. A m.f. > 1 means that a certain blood pressure change will be under estimated. A m.f. < 1 means that it will be over estimated.

Conclusion: We conclude that the wide range of the limits of agreement for both the m.f. and the constant measured during anaesthesia and surgery in two different devices casts serious doubt on the appropriateness of the oscillometric blood pressure measurement as a calibration method for noninvasive blood pressure measurement devices.

Reference:1. Bland JM et al. Statistical methods for assessing agreement between two methods of clinical measurement. Lancet 1986;1:307-310.

A.16

TECHNICAL ASPECTS OF JUGULAR BULB OXIMETRY

Cathy De Deyne, Jan Poelaert,
Johan Decruyenaere, Francis Colardyn

Department of Intensive Care, University Hospital,
Ghent, Belgium

Background and goal of study: Jugular bulb oximetry has become more and more important in monitoring ICU patients suffering from neurologic crises. Nevertheless, the technical problems resulting in insufficient reliability of the oximetry system still remain. In this paper we want to describe the possible technical adaptation in order to improve the reliability.

Methods: Retrograde catheterization of the internal jugular vein (by the Seldinger technique) is performed using a 5F introducer sheeth (length 10 cm). After in vitro calibration, the 4F opticath is introduced 13-15 cm into the sheeth until its tip is located in the jugular bulb as confirmed by fluoroscopy. During the entire monitoring time both the oximetry catheter and the introducer sheeth are continuously flushed with a heparinized solution.

Results and discussion: Using this particular setting, we analyzed the reliability of the oximetry catheter. For this purpose, 6 hourly data of 40 patients with jugular bulb oximetry during a mean course of 96.6 h, were analyzed (linear regression) by comparing the saturation values displayed by the oximetry monitor with those measured by cooximetry (Corning 2500). The correlation coefficients between saturations obtained by the direct measuring technique and cooximetry remained surprisingly high during the whole time period (r=0.987 immediately after insertion, r=0.974 during the first 24h, r=0.934 for the compiled data).

Conclusions: The jugular bulb oximetry system described seems accurate and reliable. We are furthermore convinced that the use of an "introducer" system provides the necessary stability for the extremely flexible 4F oximetry catheter and could explain the good reliablity of the whole system.

A.17

IS CORRELATION OF ARTERIAL AND END-TIDAL CARBON DIOXIDE PRESSURE DURING INHALATION ANAESTHESIA BETTER WITH LARYNGEAL MASK AS COMPARED TO FACE MASK?

D. Ivens and C. Verborgh

Department of Anaesthesiology, Free University of Brussels Medical Centre, Brussels, Belgium

Aim of this study was to compare $PaCO_2$ and $PetCO_2$ differences and correlation in patients undergoing minor surgery during inhalation anesthesia with face mask (FM) and Guedel airway (n=9) or laryngeal mask (LM)(n=9). Induction of anesthesia consisted of propofol 2 $mg.kg^{-1}$ i.v., while anesthesia was maintained with isoflurane in a O_2/N_2O mixture (FiO2=0.4) delivered trough a circle system of a CICERO respirator. $ETCO_2$, sampled at the proximal connector (LM) and between mask and elbow-piece (FM), was recorded at 4 different times. T1 : after 5 min of spontaneous ventilation, T2 : after skin incision, T3 : after 15 min surgery and T4 : after 5 min of 100% oxygen. At these times arterial blood samples were also obtained and analyzed. Other variables measured were respiratory rate (RR), minute volume (MV), heart rate (HR), mean arterial pressure (MAP), oxygen saturation (SaO_2). Statistical analysis included basic statistics. Wilcoxon signed rank test for comparison within groups and MWU-test for comparison between groups. A single regression analysis (y = ax + b) was performed and tested with ANOVA. RR was non-significantly different between the two groups, while MV was higher at T3 in the FM group. Observed $PetCO_2$ was significantly higher at T1 and T3 in the LM group as compared to the FM group, while $PaCO_2$ was non-significantly different. $P(a-et)CO_2$ was significantly higher at T1 in the FM group. Regression analysis with $PetCO_2$ as dependent variable and $PaCO_2$ as independent variable revealed a better correlation in the LM group at T1, T2 and T3 (Table). Regression on pooled data resulted in a correlation coefficient of 0.21 in the LM group and 0.62 in the FM group. Other variables were non-statistically different between the two groups. It is concluded that during isoflurane/N2O anesthesia correlation of $PaCO_2$ and $PetCO_2$ is better with a laryngeal mask as compared to a face mask.

Table

R^2	T1	T2	T3	T4
FM	2	73	52	81
LM	78	86	85	56

A.18

CARDIAC OUTPUT (CO) MEASUREMENT : COMPARISON OF ESOPHAGEAL DOPPLER (ED) VS THERMODILUTION (TD)

JY Lefrant, JE de La Coussaye, G Aya, G Saïssi, JJ Eledjam.

Dept of Anesthesiology and Intensive Care University Hospital. 30029 Nîmes. France

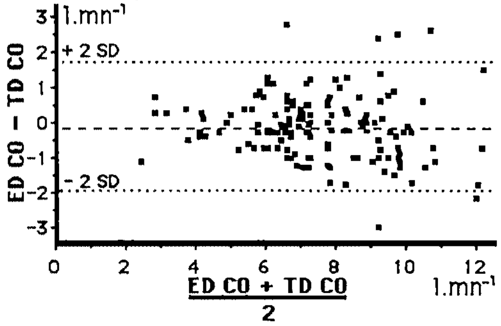
Background and goal of study : TD is the "gold standard" method to measure CO in ICU patients but can lead to serious complications(1-2). ED can measure CO with the aid of a nomogram based on age, height and weight(3). The aim of the study was to determine the accuracy of CO measured by ED vs TD.

Material and Methods : Were included 20 sedated patients under mechanical ventilation in whom Pulmonary Artery Catheter (PAC) was required. Were excluded patients with esophageal or pharyngeal diseases or surgery, with coagulopathy, with arrhythmias or those aged less than 18 years.The esophageal probe was introduced in the esophagus to measure the maximum velocity of blood flow in descending aorta. ED-CO was the product of maximum velocity determined by nomogram, aorta diameter and heart rate. TD-CO were determined by a triplicate injection of 10 ml of cold saline solution. CO measurements were simultaneously performed in blinded fashion by 2 observers when determination of hemodynamic status was required. ED-CO was always performed by the same observer after training (9 patients).

Results and discussion : 14 males, 6 females (58 ± 18 years) entered the study. ED-CO could be determined in 19 of them (95 %). 130 measurements were performed in patients in septic shock (n = 12), acute pancreatitis (n = 3), or following cardiac (n = 2) or digestive (n = 2) surgery.Regression coefficient (r^2) was 0.82. Bland & Altman test is shown in figure 1. Sensitivity (power to detect change of CO > 10% in the same way) was 75% and serious pitfall (opposite change of CO between the 2 methods) was 1,6%. (2 values).

Conclusion : CO determined by ED seems to be accurate but requires trained operator.

Figure 1. Bland & Altman test



References : (1) Perruzi et al, Curr Op Anaesth 1992 ; 5 : 11-14. (2). Shah KB et al, Anesthesiology 1984 ; 61: 271-275. (3). Singer M et al, Crit Care Med 1989 ; 17 : 447-452.

A.19

CARDIAC OUTPUT DETERMINED FROM PULMONARY GAS EXCHANGE

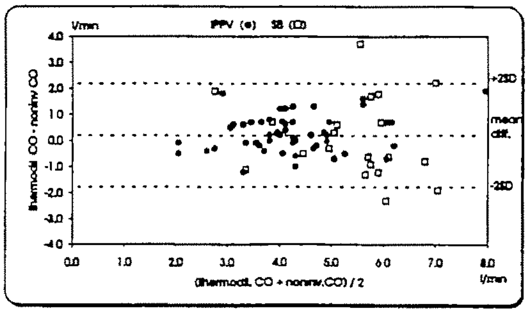
Barbro Österlund, Göran Johansson, Sebastian Reiz

Department of Cardiothoracic Anaesthesia & Surgery, University of Umeå, Umeå, Sweden.

Background and goal of study: A new system (1) by which cardiac output can be determined non-invasively (COniv) from carbon dioxide (CO2) elimination (VCO2), end-tidal CO2 tension (petCO2) and derived mixed venous CO2 tension (pvCO2) has been evaluated clinically. The goal of the study was to determine the accuracy and reproducibility of this gas exchange technique using thermodilution CO (COth) as the reference method.

Methods and patients: 35 patients were studied after institutional approval directly after cardiac surgery while sedated and mechanically ventilated (IPPV), as well as awake, extubated and spontaneously breathing (SB) 18 h later. Two COniv were obtained within 5 min during IPPV and SB. Simultaneously, 5 COth were recorded and averaged for comparison. The gas exchange system comprises a closed breathing circuit and measures oxygen uptake, VCO2 and petCO2. Periods of CO2 rebreathing are automatically implemented after a stable petCO2 level has been documented during 50 breaths and pvCO2 is extrapolated from the exponential rise of petCO2 during rebreathing. COniv is calculated as: VCO2/(petCO2-pvCO2).

Results and conclusions: 57 COniv could be obtained in the 35 patients during IPPV but only 21 in 18 patients during SB. The low number of measurements during SB was due to large variations in tidal volume and leakage around the mouth piece. Comparison of the techniques (IPPV+SB) is presented in the figure. Regression analysis showed: COniv = 0.72xCOth + 1.1, r = 0.71, p<0.05. Reproducibility of the two techniques was comparable.



We conclude that COniv had sufficient accuracy and reproducibility to be used for clinical decisions in sedated patients during IPPV whereas the performance during SB early after cardiac surgery was unacceptable.

Reference: Gedeon A, et al: Journal of Clinical Monitoring 1992. 8:267-277.

A.20

PRESERVATION OF HUMIDITY AND HEAT OF RESPIRATORY GASES IN PATIENTS WITH MINUTE VENTILATION > 10 L/MIN.

Claude MARTIN, Laurent PAPAZIAN, Gilles PERRIN,
Pierre SAUX, François GOUIN
Department of Anesthesia and Intensive Care, Hôpital Nord and
Hôpital Sainte-Marguerite - Marseille - France

Background and goal of study : the study objective was to compare the thermic and humidification capacity of one Heated Humidifier System (Bennett Cascade 2 Humidifier) and two Heat and Moisture Exchangers (Pall Ultipor and Humid-Vent Filter, Gibeck) in intensive care unit patients submitted to minute ventilation > 10 l/min.

Materials and methods : the patients were included in a prospective, controlled, randomized, not blinded study. They were patients requiring controlled mechanical ventilation with minute ventilation > 10 l/min for more than 3 days. They had to be sedated and paralyzed. Following a randomized order, the patients were ventilated for 24h periods with the Bennett Cascade 2 Humidifier and the Humid-Vent Filter. The Pall Ultipor filter was studied over a period of 45 min. In each patient, during the inspiration phase, the following measurements were performed : mean and minimum values of temperature, relative and absolute humidity of inspired gases.

Results and discussion : the Bennett Cascade 2 Humidifier and the Humid-Vent Filter had a better thermic capacity than the Pall Ultipor Filter (p < 0.001). With regard to relative humidity, no difference at any time was observed between the Bennett Cascade 2 Humidifier and the Humid-Vent Filter. The Pall Ultipor Filter achieved a lower performance when compared with the other two systems (p < 0.007). Concerning absolute humidity of inspired gases, the Pall Ultipor Filter achieved a lower performance than any other tested systems (p < 0.02). A small but significant decrease in temperature and absolute humidity, but not in relative humidity was seen after 24h of use with the Humid-Vent Filter. However, with this filter all patients had absolute humidity > 28 mg H_2O/l and relative humidity > 93% after 24 hours of use.

Conclusion : in patients with minute ventilation > 10 l/min, the Humid-Vent Filter has a thermic and humidification capability close to the reference system, the Bennett Cascade 2 Humidifier. The Pall Ultipor Filter has a significantly lower capability in these patients.

A.21

TOLERANCE OF PREOPERATIVE TRANSESOPHAGEAL ECHOCARDIOGRAPHY IN PATIENTS SHEDULED FOR AORTIC SURGERY

Marilyn Gosgnach, Françoise Le Bret, Nadia Smail,
Marc Beaussier, Pierre Viars
Department of Anesthesiology, CHU Pitié-Salpêtrière,
University Paris VI, Paris, France.

Background and goal of the study: Transthoracic echocardiography represents a non invasive approach to assess cardiac function before aortic surgery but is often inadequate because of the high rate of COPD in this population.By contrast Transesophageal echocardiography(TEE) provides high quality imaging of the heart.The aim of the study is to appreciate the tolerance of such a procedure in this high risk population.

Material and methods:31 consecutive patients scheduled for aortic surgery were included in this study.Hypertension was noted in 15 patients , clinical CAD in 12 and COPD in 11. The probe was inserted after topical anesthesia with lidocaine and midazolam sedation. Mean arterial pressure (MAP), heart rate (HR) and oxygen saturation(SaO_2) were noted before the procedure, during the probe insertion, during the examination at 2 minutes interval and 2 min after the probe removal .A computerized ST segment analysis was used to detect myocardial ischemia .

Results: The insertion of the probe provoked an increase in MAP lasting 4 minutes. Throughout the procedure the heart rate remains significantly increased. 5/31 patients developed episodes of silent myocardial ischemia, at the probe insertion (n=4) and during the procedure (n=1).They lasted less than 2 min in all but one patient in whom it persisted until the probe removal. No decrease in SaO_2 was noted .

	control	intro	intro+2	intro+4	removal	remov+2
HR(bpm)	76±14	100±20 *	91±21*	86±18*	89±20*	82±16*
MAP (mmHg)	96±16	110±20 *	105±18 *	104±18 *	93±14	89±13
SaO_2 (%)	96±2	96±2	96±2	96±2	96±2	96±2
ST< (n)	0	4	4	1	1	0

* $p<0.05$ vs control (x ± SD, ANOVA)

Conclusion: Although TEE is a very useful means to assess LV function before aortic surgery , it is associated with significant hemodynamic and ischemic ST segment changes. Control of the hemodynamic response to probe insertion seems desirable during this procedure in this patient population.

A.22

DIPYRIDAMOLE-TEE AND 24 h HOLTER-ECG AS PREOPERATIVE SCREENING TESTS FOR CORONARY ARTERY DISEASE IN PATIENTS WITH ABDOMINAL AORTIC ANEURYSM.

Margareta Östman, Mats Karling, Kjell Karp, Dag Teien and Sebastian Reiz

From the Departments of Anaesthesia and Clinical Physiology, University of Umeå, Umeå, Sweden.

Background and goal of study: Patients with aortic atherosclerotic disease have a high prevalence of covert coronary artery disease (CAD). Several adjunct tests, such as dipyridamole-thallium scintigraphy (DTS), have been proposed for risk assessment and identification of patients requiring coronary angiography. Recent studies have shown poor performance of the DTS technique in these respects (1,2). We present our *initial experience* of dipyridamole-transoesophageal echocardiography (dip-TEE) and 24 hour 2-lead Holter ST-segment recording in the detection of significant coronary artery stenosis in patients with abdominal aortic aneurysms.

Patients and methods: After institutional approval, 15 consecutive, elective aortic surgical patients were subjected to preoperative coronary angiography, dip-TEE and 24 h 2-lead Holter ECG (II + V5). Myocardial ischaemia by dip-TEE was defined as new systolic wall motion abnormalities (SWMA-s) developing during low (0.56 mg/kg) or high (0.80 mg/kg) iv dip infusion and by Holter ECG as a reversible ST-segment depression of 0.2 mV or more recorded in at least one lead. A significant coronary stenosis was defined as an obstruction of the diameter of at least one vessel by 50% or more. The indication for coronary intervention was based on the angiographic findings independently of the results of the two other tests.

Results and conclusions:

	n=	*Pos. dip-TEE*	*Pos. Holter*
no CAD	**4**	**2**	**1**
CAD			
<50%	**1**	**0**	**0**
>50%	**10**		
CABG/PTCA indic.	**5**	**4**	**5**
Not indicated	**5**	**0**	**0**

We conclude that the *positive and negative predictive power* of dip-TEE (pos./neg.: *67%/89%*) and Holter ECG (pos./neg.: *83%/100%*) in identifying aortic surgical patients with indications for CABG or PTCA, found in this pilot study, are sufficiently high to warrant further studies of these techniques in this patient population.

References: 1. Baron J-F, et al, Anesthesiology 1991, 75:A100. 2. Bertrand M, et al, Anesthesiology 1990, 73: A86.

A.23

EVALUATION OF HAEMODYNAMIC INDICES OF MYOCARDIAL ISCHAEMIA IN PATIENTS WITH CORONARY ARTERY DISEASE (CAD)

Per Hohner, Göran Johansson, Sören Häggmark, Vipin Mehta, Sebastian Reiz

From the Department of Cardiothoracic Anaesthesia & Surgery, University of Umeå, Umeå, Sweden.

Background & goal of study: Haemodynamic indices such as rate pressure product (RPP=SAPxHR), pressure rate ratio (P/R=MAP/HR) and pulmonary arteriolar occluded pressure (MPAOP) are regarded as valuable adjuncts to ECG monitoring to indicate when the risk for myocardial ischaemia (MI) is increased (1,2). This study evaluates the sensitivity and specificity of RPP, P/R and MPAOP for MI provoked by atrial pacing and blood pressure (BP) manipulation in patients with CAD.

Patients & methods: Sixteen patients with proximal LAD stenosis were studied during general anaesthesia prior to coronary surgery. MI was induced by step-wise increase in HR by atrial pacing, while BP was kept constant. After recovery, and with HR kept at control level by pacing, blood pressure was increased (BP↑) or decreased (BP↓) in a random fashion to the same RPP and P/R as at end-point pacing by the use of phenylephrine and nitroprusside, respectively. MI was defined as a change of the spatial ST-segment vector magnitude (STC-VM) >50 uV and/or myocardial lactate production. Myocardial oxygen consumption (MVO2) was derived from coronary blood flow by thermodilution and arterio-coronary sinus oxygen content differences at each measurement. Values of haemodynamic indices tested for sensitivity and specificity were: RPP>12.000, P/R<1.0 and MPAOP>15 mm Hg.

Results & discussion: Eighty measurements were analyzed (16 controls, 16 pacing-induced MI, 16 at the pacing step prior to MI, 16 at BP↑ with 3/16 MI, and 16 at BP↓ with 3/16 MI). MVO2 was lower at the MI threshold than at BP↑ (10.1±7.2 vs 12.7±6.0 ml/min, $p=0.030$) but higher than awake (8.2±5.4 ml/min, $p=0.009$). MVO2 during BP ↓ (5.9±2.4 ml/min) was lower than awake ($p=0.044$). Sensitivity/specificity: RPP: 27%/83%, P/R: 77%/55%, MPAOP: 5%/95%. We conclude that P/R is a moderately useful haemodynamic index of MI during tachycardia with normal BP but not during hypotension with normal HR. A major reason for this discrepancy, observed despite a lower P/R during BP↓ (0.70±0.13 vs 0.86±0.08, $p<0.001$), is that MVO2 at BP↓ was only 60% of the value during pacing-induced MI. Although specific, neither RPP, nor MPAOP are sufficiently sensitive indices of MI.

References: (1) Kaplan JA, Wells PH: Anesth Analg 1981; 60:789, (2) Buffington CW: Anesthesiology 1985, 63:651.

A.24

THE USE OF THE CUSUM PLOT FOR DETERMINATION OF MYOCARDIAL ISCHAEMIA THRESHOLD DURING ATRIAL PACING IN PATIENTS WITH CORONARY ARTERY DISEASE.

Sebastian Reiz, Göran Johansson, Per Hohner, Sören Häggmark

From the Department of Cardiothoracic Anaesthesia and Surgery, University of Umeå, Umeå, Sweden.

Background and goal of study: Myocardial lactate extraction (MLE) data used to diagnose myocardial ischaemia clinically are difficult to interpret for several reasons; *First,* lactate is used as a substrate at the same time as it is released at the onset of ischaemia; *second,* blood sampled in the coronary sinus might not include outflow from the ischaemic territory, or might be diluted from non-ischaemia territories, *third,* flow through an ischaemic territory may be too low, or the ischaemic territory too small, to offset a clear decrease in MLE. The true incidence of ischaemia will hence be underestimated if myocardial lactate production (MLP) is used as an index of ischaemia (1). The goal of the study was to analyse if the CuSum plot, a graphical statistical technique (2) which enhances trend changes, could indicate the onset of lactate release, measured as MLE, during atrial pacing. Simultaneously, we performed the same test using a vectorcardiographic (VCG) ST-segment criterion for ischaemia.

Patients and methods: After institutional approval and informed consent, 15 patients with predominant LAD stenosis were studied during general anaesthesia prior to coronary surgery. They were subjected to incremental increase in heart rate by atrial pacing at constant blood pressure till arterio-great cardiac venous blood analysis demonstrated, MLP. A computerised VCG was analysed for changes in STC-VM (change of spatial ST-vector magnitude). In patients with CAD, a change of STC-VM >50 uV is indicative of ischaemia. Numerical values of MLE and STC-VM were entered in the CuSum plot in which the third of the five or six pacing step values was used as the reference point.

Results and conclusions: The start of lactate washout could be easily identified by the CuSum plot in all patients. It coincided with MLP in 2/15 only (MLE=10.4±10.0% vs 13.3±7.0% at control, means±SD, n.s.) and abnormal STC-VM (75±37 uV vs 9±4 at control, $p<0.01$) in 12/15. At the next pacing step, 8/15 had MLP (MLE 0.7±7.3%, $p<0.01$ vs control) and 15/15 had abnormal STC-VM (117±41 uV, $p<0.01$ vs control). At the last pacing step, MLE was -3.1±4.0% and STC-VM 131±45 uV. We conclude that the CuSum plot is sensitive for identification of ischaemic threshold during atrial pacing, using MLE as an index of ischaemia. VCG STC-VM is, however, significantly more accurate ($p<0.0001$ at the ischaemia threshold and $p=0.003$ at the next step) than MLE for this purpose.

References: (1) Häggmark S, et al: Anesthesiology 1989, 70:19. (2) Wohl H: N Engl J Med 1977, 296:1044.

A.25

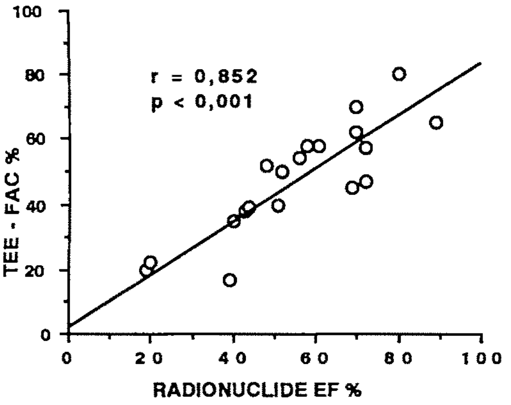
EVALUATION IN INTENSIVE CARE OF THE FRACTION AREA CHANGE OBTAINED BY AUTOMATIC BORDER DETECTION.

N. Liu*, P. Catoire*, J. Rosso**, M. Saada#,
F. Bonnet.*
* Réa Chir ** Nuclear Med H. Mondor hospital, 94010
Créteil France, # DAR, Pitié Paris France.

The manual measurement of the fraction area changes (FAC) of the left ventricule obtained by trans-esophageal echocardiography (TEE) has been documented to be correlated with isotopic ejection fraction (EF)[1]. An echographic Automatic endocardial Border Detection algorithm (ABD) is now available, allowing to calculate on-line FAC [2]. The aim of this study was to compare the FAC obtained by ABD with isotopic EF

Methods : 10 mechanically ventiled critical ill patients were studied. Simultaneous, TEE and radionuclide images were obtained with Technetium 99m in each patient, before and after dobutamine(5 mcg/kg/min). The set was performed in radionuclide imaging unit. FAC were measured at the midpapillary muscle level. TEE used a 5-MHz oesophageal trans-ducer (Hewlett-Packard Sonos 1000 Andover®).

Results : The figure shows the correlation between FAC measured by ABD and EF measured by radionuclide (r=0,85). Bias (FAC-EF), precision, and agreement coefficient R with and without bias correction are summarized in the table.



	Bias	Precision	R	R Limits
FAC vs EF	-9,4	9,84	0,74	0,88-0,45
FAC vs EFcorr	-0,4	9,84	0,85	0,94-0,67

Discussion : A good agreement was obtained between FAC and isotopic EF. Agreement increased after Bias correction. We conclude that FAC obtained by ABD is accurate for the EF evaluation in ventilated patients.

1/ Urbanowicz et All : Anesthesiology 1990; 72, 607-612.
2/ Pérez et All : JACC 1992; 19, 313-320.

A.26

SENSITIVITY AND SPECIFICITY OF MECHANICAL AND ELECTROCARDIOGRAPHIC MYOCARDIAL ISCHAEMIA (MI) MONITORING TECHNIQUES.

Per Hohner, Vipin Mehta, Michel Saada, Sõren Häggmark, Erica Jansson, Gõran Johansson, Sebastian Reiz

Department of Cardiothoracic Anaesthesia and Surgery, University of Umeå, Umeå, Sweden and Department of Anaesthesia, Pitié-Salpêtirère Hospital, Paris, France.

Background & goal of study: New systolic wall motion abnormalities (SWMA) by transesoephageal echocardiography (TEE) are generally considered as the most sensitive and specific indicator of myocardial ischaemia (MI) (1). Recent animal data have documented lack of specificity with increased loading conditions (2). The goal of this study was to determine the sensitivity and specificity of TEE, 12-lead ECG (ECG) and computerized vectorcardiography (VCG) for MI during atrial pacing and changing loading conditions, using myocardial lactate production (MLP) as the end-point for ischaemia.

Materials and methods: 14 patients with proximal LAD stenosis were studied during anaesthesia prior to coronary surgery. They were subjected to stepwise increase in heart rate by atrial pacing (AP) till MLP. After recovery, they were randomly subjected to elevation and reduction of blood pressure (BP↑/BP↓) by phenylephrine and sodium nitroprusside to rate pressure products and pressure-rate ratios identical to those obtained at end-point pacing respectively. A deterioration of regional LV function by at least 2 steps on a 5 degree scale, in at least 1/4 segments of the cross-sectional image at the mid-papillary level was considered as MI by TEE. The ECG criterion was a new horizontal or downsloping ST-segment depression >0.1 mV, 60 msec after the J-point. The VCG criterion was a change of the spatial ST-segment vector magnitude (STC-VM) >50 uV, 60 msec after the J-point.

Results & discussion: 16 episodes of MLP (AP:14, BP↑ :1, BP↓:1) were recorded during the 42 measurements. Sensitivity/specificity:ECG: 69%/100%, VCG: 88%/96%, TEE: 50%/92%. During AP, ECG, VCG and TEE were positive for MI before MLP occurred in 5/14, 11/14 and 4/14 respectively. TEE was positive for MI before ECG or VCG in 2/14. We conclude: (1) TEE is less sensitive and not more specific than ECG/VCG techniques in detecting MI by MLP, (2) MLP is a late indicator of MI. Possible reasons for lack of TEE sensitivity: (a) the ischaemic area was not sampled at the midpapillary level (b) interpretation of new SWMA-s during tachycardia is difficult.

References: (1) Smith JS, et al: Circulation 1985; 72:1015. (2) Buffington CW, et al: Anesthesiology 1991; 75:464.

A.27

PULMONARY AND SYSTEMIC VASCULAR EFFECTS OF ISOPROTERENOL, NITROGLYCERIN AND PROSTAGLANDIN E1 EARLY AFTER CARDIAC OPERATIONS IN PATIENTS WITH PULMONARY HYPERTENSION

J Alvarez, ML Camara, J Cortiñas, J Cortes, A Aris

Department of Anaesthesiology, Hospital Xeral De Galicia, Santiago De Compostela & Cardiac Surgery Unit, Hospital De La Santa Creu I Sant Pau, Barcelona, Spain

Background and goal of study: Patients with mitral stenosis and some degree of right ventricular failure may benefit from inotropic or pulmonary vasodilator drugs in the early postoperative period.

Materials and methods: 40 patients undergoing surgery for mitral stenosis were randomized to four groups: "C" (n=10) no drugs, "I" (n=10) isoproterenol 5 ng/kg/min, "N" (n=10) nitroglycerin 0.5 ug/kg/min and "P" (n=10) prostaglandin E1 0.08 ug/kg/min. After 18 h, the vasoactive drugs were reduced to 1/2 of the initial dose and 3 h later they were discontinued. Measurements of haemodynamics including cardiac index (CI), systemic vascular resistance (SVR) and pulmonary vascular resistance (PAR) were made after surgery without drugs (D0), and 1h (D1), 12h (D2), 18h (D3), 21h (D4) and 24h (D5) after institution of the respective drug.

Results: * denotes p<0.05 compared with group "C".

	D0	*D1*	*D2*	*D3*	*D4*	*D5*
PAR (Wood Units)						
"C"	**3.9±2.4**	**4.5±1.8**	**3.9±3.1**	**3.3±2.0**	**2.9±2.3**	**3.2±1.4**
"I"	**4.8±4.3**	**3.1±2.7**	**3.3±3.3**	**3.6±3.0**	**3.6±3.3**	**4.6±4.1**
"N"	**3.2±2.4**	**3.1±2.4**	**2.3±1.4**	**2.5±1.5**	**2.3±1.3**	**2.4±1.8**
"P"	**3.2±1.2**	**2.5±0.8***	**1.7±0.5***	**1.6±0.5***	**1.7±0.5**	**1.9±0.8**
SVR (Wood Units)						
"C"	**31.9±9.5**	**33.5±9.0**	**22.9±7.4**	**19.4±5.7**	**18.6±4.4**	**20.2±4.1**
"I"	**27.0±9.4**	**22.5±6.9***	**16.8±4.3**	**18.2±5.8**	**17.6±5.9**	**19.0±5.9**
"N"	**23.0±7.0**	**22.1±7.5***	**17.2±3.9**	**13.5±6.0**	**15.8±7.1**	**15.8±9.2**
"P"	**26.5±7.9**	**24.7±7.9**	**18.1±4.6**	**14.7±4.5**	**16.9±4.5**	**18.7±3.8**
CI (l/min/m2 BSA)						
"C"	**1.3±0.3**	**1.3±0.3**	**1.9±0.4**	**2.4±0.5**	**2.3±0.3**	**2.3±0.3**
"I"	**1.5±0.5**	**2.1±0.4***	**2.6±0.4***	**2.6±0.7**	**2.7±0.8**	**2.2±0.6**
"N"	**1.8±0.4**	**2.0±0.5***	**2.5±0.5**	**3.2±0.9**	**3.0±1.0**	**2.8±0.8**
"P"	**1.5±0.3**	**1.7±0.5**	**2.2±0.6**	**2.7±0.7**	**2.3±0.5**	**2.2±0.4**

Conclusions: A low dose of prostaglandin E1, which at this dose has no effect on platelet aggregation or systemic vascular tone, effectively decreases pulmonary vacular resistance in patients operated on for mitral stenosis.

Reference: Camara ML, et al: Hemodynamic effects of prostaglandin E1 and isoproterenol early after cardiac operations for mitral stenosis. J Thorac Cardiovasc Surg 1992; 103:1177-1185.

A.28

ECHOCARDIOGRAPHIC STUDY OF THE INDUCTION WITH A LOW-DOSE OF SUFENTANIL FOR CORONARY ARTERY SURGERY

N. Bromberg, C. Decoene, E. Chammas, A. Pol,
R. Krivosic-Horber

D.A.R.C. 1, Hopital B, CHRU de LILLE,
59037 LILLE CEDEX. FRANCE.

BACKGROUND AND GOAL OF STUDY : Sufentanil has the advantage of shorter recovery time and less postoperatively respiratory depression than fentanyl when it is used for coronary artery bypass grafting (CABG) surgery (1). Because increasing the dose of sufentanil does not produce a dose related suppression of hemodynamic and hormonal responses to surgical stimulation, some investigators have suggested that smaller doses of sufentanil should be used (2). This study was designed to evaluate the hemodynamic responses of a low dose of sufentanil throughout the induction.

MATERIALS AND METHODS : Ten patients scheduled for an elective CABG surgery whose resting left ventricular ejection fraction (EF) was greater than 50% were studied. Preanesthetic medication consisted of scopolamine and midazolam. Prior to induction, 500 ml of Haemaccel^{r} was infused. Anesthesia was induced with pancuronium (0,1mg/kg) and **sufentanil 5mcg/kg in 5 minutes.** Cardiac output (CO) and EF were monitored by trans-thoracic echocardiography. Hemodynamic measurements (Mean Arterial Pressure, Heart Rate, CO, EF) were taken just before induction (T1), at the end of sufentanil infusion (T2), after intubation (T3), and 20 minutes after infusion of sufentanil and before surgery (T4). Anesthesia was maintained with 50% nitrous oxide and an infusion of 0,1mcg/kg/min of sufentanil continued until just prior to the institution of cardiopulmonary bypass, with a bolus (50 or 100mcg) of sufentanil before the sternotomy, with additional bolus of sufentanil (50mcg) given whenever MAP reached >20% above preanesthetic values. The total amount of sufentanil administered was 21,8 +/- 2,1 mcg/kg. Postoperatively, the patients were transferred to Surgical Intensive Care Unit (SICU) where segment ST changes were assessed and mechanical ventilation was performed until awakening. Statistical analysis used the Wilcoxon matched-pairs signed ranks test ; p<0,05 was accepted as significant.

RESULTS AND DISCUSSION : The hemodynamic measurements taken throughout the induction are reported in the table1. HR and CO increased slightly after intubation. This hemodynamic stability corresponds to the stability reported by Thomson using 15mcg/kg of sufentanil (1) and by Philbin using 10, 20, or 30mcg/kg of sufentanil (2). The patients were ready for extubation 877 +/- 257 min after their arrival in SICU.

CONCLUSION : In conclusion, a low dose of sufentanil can be administered with adequate hemodynamic effects and without the need of any other hypnotic and allows an earlier awakening and extubation.

REFERENCE
1-Can. J. Anaesth., 1987, 34 : 227-232.
2-Anesthesiology, 1990, 73 : 5-11.

TABLE 1 : HEMODYNAMIC VALUES THROUGHOUT INDUCTION
* : p<0.05 between successive measurements

	MAP(mmHg)	HR(/min)	CO(l/min)	EF(%)
T1	97(15)	58(7)	5.3(0.7)	60(4)
T2	90(18)	61(11)	4.9(1)	56(5)*
T3	95(21)	66(13)*	5.6(1.2)*	58(5)
T4	83(10)*	61(11)*	5.1(0.7)*	57(3)

A.29

GASTRIC MUCOSAL PERFUSION IS BETTER PRESERVED DURING CARDIAC SURGERY WHEN ISOFLURANE RATHER THAN ENFLURANE OR PROPOFOL IS USED TO MAINTAIN ANAESTHESIA.

Monty Mythen, Deborah Browne, Colin Hamilton-Davies, Andrew Webb. The Bloomsbury Department of Intensive Care and The Department of Anaesthesia, The Middlesex Hospital, London, UK

Background and goal of study: We have previously shown that peri-operative gastric mucosal hypoperfusion is associated with a poor outcome following elective major surgery [1]. The aim of this study was to compare the effects of propfol, isoflurane and enflurane on gut mucosal perfusion in patients undergoing elective coronary artery bypass graft surgery (CABG).

Materials and methods: 30 patients with good pre-operative ventricular function undergoing elective CABG. Routine measurements of heart rate (HR), blood pressure (BP) and right atrial pressure (RAP) were made. In addition cardiac output (CO) and stroke volume (SV) were determined by oesophageal Doppler measurement of aortic blood flow and gastric mucosal perfusion by tonometric assessment of gastric mucosal pH (pHi). Patients were randomised following admission to the trial to receive either Enflurane (group E [n=10]), Isoflurane (group I [n=10]) or Propofol (group P [n=10]) for maintenance of anaesthesia. Otherwise patients were managed according to a standard anaesthetic protocol.

Results: There were no significant differences in demographic details or baseline values for mean HR, BP, CO, SV, RAP or pHi between the three study groups. In all 3 groups BP was unchanged from baseline to end of surgery. Group I patients maintained their mean pHi from baseline to end of surgery and demonstrated a significant rise in CO ($p < 0.05$) and SV ($p < 0.05$). Group E and P patients had significant reductions in mean pHi from baseline to end of surgery ($p < 0.01$). In group E patients there was a significant increase in CO ($p < 0.05$), HR ($p < 0.001$) and RAP (0.05) but no change in SV. In group P patients there was a significant increase in HR ($p < 0.01$) but no change in CO, SV or RAP.

Conclusion: Patients are more likely to maintain gastric mucosal perfusion during elective CABG if anaesthesia is maintained with Isoflurane rather than Enflurane or Propofol as part of a balanced anaesthetic technique.

Reference: 1.Mythen MG and Webb AR. Gastric mucosal ischaemia associated with major complications and death following routine major surgery. *Gastroenterology* 1992; 4: A.227.

A.30

PROPOFOL/FENTANYL-ANESTHESIA IN PATIENTS WITH HIGHLY DEPRESSED CARDIAC FUNCTION

Helmut Rauch, Franz Fleischer, Rainer Haußmann, Bernd Böttiger, Eike Martin

Dpt. of Anaesthesiology, University of Heidelberg, Germany

Background and aim of study: Our aim was to study whether hypotensive phases during Propofol/Fentanyl anesthesia in patients with reduced cardiac function could be avoided by pre-induction volume loading or whether catecholamines are still required.

Materials and methods: Before anesthesia was induced, 13 patients (ASA III-IV with highly depressed cardiac function), who were undergoing implantation of an automatic defibrillator, were catheterized under local anesthesia with a 20 G cannula (left radial artery) and a rapid response thermistor Swan Ganz^{R} catheter (right internal jugular vein). 10 ml/kg of Ringer's solution was infused and anesthesia was induced with 15mg/min Propofol (Disoprivan^{R}, ICI Pharma) and 0,1 - 0,2 mg Fentanyl^{R} (Janssen). At preset time intervalls (T1: pre induction, T2: shortly before intubation, T3:immediately after intubation, T4: 5 min. after intubation, T5: steady state, T6: before skin incision, T7: 5 min. after skin incision, T8: at the end of defibrillations) heart rate (HR), mean arterial pressure (MAP), mean pulmonary arterial pressure (MPAP), PAWP, CVP, cardiac index (CI) and right ventricular ejection fraction (RVEF)were measured. From these data right ventricular enddiastolic volume index (EDVI) and systemic vascular resistance (SVR) were calculated. CI and RVEF were measured using a computer (Explorer^{R}, Baxter Ltd.)

Results and discussion: There was an evident decrease of MAP after induction and during maintenance of anesthesia. At the same time MPAP increased. PAWP increased in only one case. CI decreased continously, whereas SVR decreased for only a short period after induction. The right ventricular parameters were stable at all times.

These results are similar to those found by Haessler et al (1992) in a comparible group of patients.

Conclusion: Decrease of MAP and CI in critically ill patients under Propofol/Fentanyl anesthesia cannot be avoided even by sufficient pre infusion of volume. Therefore use of catecholamines and installation of invasive monitoring seemes to be justified.

Reference: Haessler, R. et al:Propofol/fentanyl versus etomidate/fentanyl for the induction of anaesthesia in patients with aortic insufficiency and coronary artery disease. J Cardiothorac Vasc Anesth 1992; 6(2): 173-80

A.31

ACCURACY OF PROCESSED AUDITORY EVOKED RESPONSE IN PREDICTING MOVEMENT DURING CARDIAC SURGERY

H. Kuppe, K.-F. Klotz, S. Eleftheriadis, H. Gehring, W. Gerling
Department of Anesthesiology, Medical University of Luebeck, Germany

INTRODUCTION: Processed EEG has been used to assess anesthetic adequacy. The auditory evoked response has been shown to correlate with the levels of anesthetic agents. No study has examined the correlation of processed auditory evoked potential (AER) variables in response to surgical procedures. The purpose of this study was to determine whether processed variables such as the spectral edge frequency (SEF) and mean frequency (MF) provides additional information about anesthetic depth in patients undergoing cardiac surgery.

METHODS: After Human Investigation Committee approval and informed consent auditory evoked potential monitoring was performed in 30 patients undergoing cardiac surgery. After premedication with flunitrazepam anesthesia was induced with fentanyl. After tracheal intubation with pancuronium the lungs were ventilated with air-O2 without inhalational agents. Additional fentanyl (0.5 µg*kg^{-1})and flunitrazepam (0.5 mg) was given before skin incision, sternotomy, and aortic-atrial cannulation. AERs were recorded using a Nicolet Pathfinder. Impulse: binaural click (70 dB); rate: 9.7 Hz; derivation: Cz (pos), A1/A2 (neg); filter: 5-1000 Hz. In order to achieve a result from 2.5 Hz for each spectral analysis the timebase was lenghtened and stimulated fourfold, whereby 4 AERs were registered. Recordings were obtained continously from the waking state.

RESULTS: The following phases were investigated: T1 (awake), T2 (after induction), T3 (hypothermia), T4 (after extracorporal circulation), T5 (during intraoperative movement). The characteristic peak latencies (V, Pa, Nb) and the AER variables like SEF and MF are shown in the **table**: Latency values (*=p<0,01).

table	T1	T2	T3	T4	T5
V (msec)	6.1±0.1	7.0±0.1•	9.1±0.2•	7.1±0.1	6.9±0.3
Pa(msec)	29.4±0.4	34 3±0.5•	41 2±0.9•	32.9±0.4•	31.0±1.3
Nb(msec)	43.8±1.5	54.9±1.2•	64.3±1.1•	52.4±0.8•	47.8±2.7
SEF (Hz)	49.0±1.7	36.3±1.2•	28.1±1.7•	39.6±1.4•	43.6±2.5
MF (Hz)	22 0±1 3	16.8±0.4•	13.3±0 5•	17.3±0.7•	18.6±1.1

DISCUSSION: Latency measurements obtained from AEP recording present a possibility to predict intraoperative movement, which was observed in four patients. Assessment of processed AEP variables such as SEF and MF appears to enhance further diagnostic accuracy as this data supports the concept of a relationship between AEP and anesthetic depth. Advanced signal processing methods can provide guidelines to the administration of anesthesia in order to prevent intraoperative arousal.

A.32

CEREBRAL BLOOD FLOW VELOCITIES (CBFV) DURING ANAESTHESIA FOR GYNAECOLOGICAL LAPAROSCOPIC SURGERY.

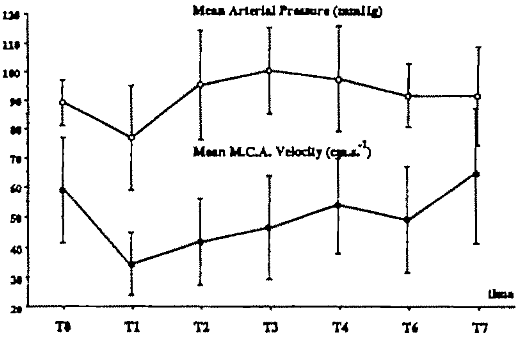
Jean Claude Granry, Christine Monrigal,
Jean Paul Jacob, Jean Pierre Monrigal

Department of Anaesthesia and Intensive care
University of Angers, Angers, France

Goal of Study : The increase of the abdominal pressure and the pneumoperitoneum during laparoscopic surgery (and anaesthesia for these procedures) induce hemodynamic and respiratory changes. We investigated these consequences on cerebral circulation using transcranial doppler sonography (TCD).

Materials and methods : 11 fully informed patients (age : 33,8 ± 8,4 yrs. weight : 54,9 ± 10,1 kg) scheduled to undergo pelvic laparoscopic surgery were enrolled in this study. The same anaesthesia was given to all patients, induced with midazolam, propofol, fentanyl and atracurium, and maintained with nitrous oxide (50 %) in oxygen and propofol (5 mg.kg^{-1} h^{-1}). Aftor intubation, ventilation was adjusted to keep PetCO$_2$ between 30-35 mm Hg. HR, NIBP, SpO$_2$ and PetCO$_2$ were monitored continuously . TCD (EME TC 2-64 device) measurements (systolic Vs, mean Vm, diastolic Vd velocities and resistance index RI) were obtained from the middle cerebral artery (MCA) before induction (T0), after induction (T1), after peritoneal insufflation with CO$_2$ (T2), after trendelenbourg position (T3), after exsufflation (T4) and after extubation (T7). Statistical analysis was performed with Kruskal-Wallis test.

Results and discussion : Following induction of anaesthesia and institution of hyperventilation, MAP and Vm decreased in all patients. At any time studied, the values were less but not significantly different than baseline (fig).



Conclusion : the results of this study indicate that there is no significant effect of laparoscopic procedures in these conditions on cerebral blood flow velocities of MCA studied by TCD.

Reference : Ho HS, et al: Intraperitoneal carbon dioxide insufflation and cardiopulmonary functions.
Arch Surg. 1992 ; 127: 928-933

A.33

NEUROENDOCRINE CHANGES DURING PNEUMOPERITONEUM FOR LAPAROSCOPIC CHOLECYSTECTOMY.

J. Joris, M. Lamy

Department of Anaesthesia, CHU Liège,
B - 4000 Liège (Belgium).

Background and goal of study: Haemodynamic changes induced by pneumoperitoneum result from mechanical factors, but probably also from humoral factors (1,2). This study investigated neuroendocrine changes during laparo-scopy, which might contribute to these haemodynamic changes and more particularly to the increase in systemic vascular resistance (SVR).

Materials and methods: 10 (9F-1M; aged 45±5) ASA I patients without cardiac pathology or medications scheduled for elective laparoscopic cholecystectomy were included in the study. General anaesthesia was induced with sufentanil 15-20 µg, thiopental 5 mg/kg and atracurium 0.5 mg/kg and maintained with $N2O:O2$ (50%) and isoflurane as needed. Ventilation was adjusted to keep end-tidal PCO_2 between 30-40 mmHg. Arterial blood samples were collected before induction (T1), 10 min after the induction, 10 min after tilting in the 10° head-up position (T3), 5 min (T4), 15 min (T5) and 30 min (T6), after the beginning of intraabdominal insufflation (14 mmHg) and 30 min after exsufflation (T7).Cortisol (CORT), renin, vasopressin (VASO), endothelin (ENDO) were measured using a RIA, and adrenaline (ADR) and noradrenaline (NA) using a HPLC. Data were analyzed by ANOVA followed by Newman Keul's test.

Results: Induction of pneumoperitoneum rapidly resulted in a massive release of VASO. VASO then decreased but remained above 20 pg/ml, the lowest plasma concentration for VASO to produce vasoactive effect. The profile of VASO release parralleled the time couse of SVR previously reported (1). Plasma concentrations of renin catecholamines also increased during pneumoperitoneum, but, these changes did not correlated with changes in SVR. Plasma concentration of ADR remained stable during pneumoperitoneum, and then further increased during recovery from anaesthesia. Increase in plasma concentrations of NA and renin rather reflected the stress response to surgery since they have similar time-course as CORT. Finally, ENDO did not change significantly during pneumoperitoneum.

	T1	T2	T3	T4	T5	T6	T7
VASO:pg/ml	3	7	2	175*	146*	43	22
ADR:ng/l	56	36	39	181*	196*	172*	556*
NA:ng/l	224	222	281	408*	486	470	489*
RENIN:pg/ml	11	13	25*	35*	51*	61*	38*
CORT: µg/l	67	53	82	107	175*	258*	287*
END:fmol/ml	26	24	25	23	20	30	30

*=$p<0.05$ as compared with T1

Conclusions: Several humoral factors might contribute to the haemodynamic changes during pneumoperitoneum. VASO, however, appears as a good candidate to explain the increase in SVR.

References: 1. Anesthesiology 1992,75:A69; 2. Can J Anaesth 1990, 37: 46.

A.34

INFLUENCE OF PNEUMOPERITONEUM AND POSTURE ON HEMODYNAMIC AND STRESS RESPONSES DURING ANAESTHESIA FOR LAPAROSCOPIC SURGERY

Suzanne Odeberg, Olle Ljungqvist, Per Gannedahl,
Torgny Svenberg, Alf Sollevi.

Departments of Anaesthesia and Intensive Care, Huddinge University Hospital and Karolinska Hospital, Stockholm.

Background and goal of study: The use of pneumoperitoneum (PP), i.e. gas insufflation into the abdominal cavity, is increasingly used to improve surgical conditions. The physiological influence of PP is however not fully examined in humans. The present study investigates the influence of PP, and its combination with different body positions, on hemodynamics and on stress response.

Materials and methods: Patients without cardio-pulmonary disease (n=11, age 18-57 yrs) were studied by Swan-Ganz and radial arterial catheterisation, before and during laparoscopic cholecystectomy, under propofol-fentanyl anaesthesia with controlled ventilation. Mean arterial pressure (MAP), myocardial filling pressures (PCWP and RAP, measured with transducers at the level of the right atrium), and cardiac output (CO, transformed to CI) were determined in the horisontal position, with a 15-20° head-down tilt, and with a 15-20° head-up tilt. The measurements were repeated after insufflation of carbon dioxide to an abdominal pressure of 12-13 mm Hg. During surgery (duration range 1-2,5 h), measurements were performed at 30 minute intervals. Blood samples for analysis of arterial plasma catecholamines and cortisol were collected before anaesthesia, repeatedly during surgery, and postoperatively.

Results: The filling pressures were strictly dependent on body position. Alterations in body position, with or without PP, did not influence CI. PP during the horisontal position increased PCWP and RAP by approximately 40% ($p<0,01$) and MAP by approximately 30% ($p<0,01$). When PP was combined with a head-down tilt, there was a further increase in filling pressures by approximately 40% ($p<0,01$), while the reduction in filling pressures during the head-up tilt was counteracted by PP. During PP with a head-up tilt, the filling pressures were not different from the horisontal position without PP. The levels of catecholamines and cortisol were low throughout the investigation.

Conclusions: Alteration in body position as well as PP causes marked changes in myocardial filling pressures. The combination of PP and a head-up tilt is associated with normal filling pressures and stable myocardial function during surgery. It is suggested that prolonged PP, especially when combined with a head-down tilt, may be hazardous in subjects with compromised myocardial function. Laparoscopic cholecystectomy is associated with a low stress response as reflected by catecholamines and cortisol.

A.35

EFFECTS OF PLASMA VOLUME SUBSTITUTION ON RIGHT VENTRICLE VOLUMES AND FUNCTION USING ELOHES® AND PLASMION®.

JY Lepage, F Garrec, JM Malinovsky, A Cozian,
and M Pinaud.
Department of Anaesthesiology, Hôtel-Dieu, 44035
Nantes, France.

Background and goal of study: The choice of which fluid to give a patient for plasma substitution during major surgery remains controversial. Hydroxyethylstarch seems to be interesting in terms of volume expansion. duration of action, side effects and cost as compared with others colloid substitutes. The role of right ventricle during hypovolaemia and acute volume loading is important to consider. Thus we investigated right ventricular volumes and function following calibrated fluid resuscitation with Elohes® (E) and Plasmion® (P) in hypovolaemic surgical patients.

Materials and methods: After institutional approval and informed consent, 20 ASA III patients recovering from major urologic surgery were randomly and equally assigned to two groups to receive 500 ml of either E or P on a ante brachial vein for 15 minutes using an infusion pump. Monitoring was obtained from EKG, Swan Ganz equipped with a fast response thermistor and radial artery cannula. Inclusion criteria consisted of fluid deficit of 500 to 1000 ml, and a 20% decrease from preoperative values in central venous pressure, pulmonary wedge pressure and end-diastolic volume, in patients fully awake with removed endotracheal tube and normal body temperature. Seven series of measurements were made before (baseline), during (5,10,15 min) and after (30 min, 1 and 3 hours) volume expansion. At the same times, blood samples were withdrawn for plasma ANF determination. After transformation in % change from baseline statistics were carried out using ANOVA with repeated measures.

Results: The main results are summarised in the table.

		baseline	15 min	3 hours
HR	P	88±7	86±5	90±6
(b. min-1)	E	91±6	90±4	89±5
MAP	P	85±5	88±5	88±5
(mmHg)	E	78±5	83±5	83±4
PCWP	P	5±1	12±1‡	6±1†
(mmHg)	E	3±1	12±2‡	7±1†
SI	P	50±3	65±4‡	53±3‡
(ml. m-2)	E	38±3§	52±5‡	46±5‡
EDVI	P	107±7	139±8‡	110±8‡*
(ml. m-2)	E	78±10§	114±15‡	100±13‡*§
EF	P	50±2	48±2	50±2
(%)	E	52±3	49±2	49±2
O^2 systemic	P	16.7±2.1	16.2±2.2	14.8±1.3†
transport	E	10.0±1.4	14.6±3.4	14.5±3.3†§
ANF	P	55±16	78±22	85±24†
(pg. ml-1)	E	54±10	102±36	99±20†

mean ± SE; † $p< 0.05$; ‡ $p< 0.01$ vs. baseline; * $p<0.01$ vs. 15 min; § $p< 0.05$ E vs. P

Discussion and conclusion: During volume expansion indicators of preload increased similarly in the two groups. Three hours after volume expansion, end-diastolic volume and systemic oxygen transport remained higher in E group than in P group, suggesting a longer duration of action of volaemic expansion.

A.36

ALTERNATING RIGHT TO LEFT VENTRICULAR EJECTION; THE CASE OF OCCULT CARDIAC TAMPONADE.

Charissios Skourtis, Lazaros Karalazos, Demetrios Setzis.

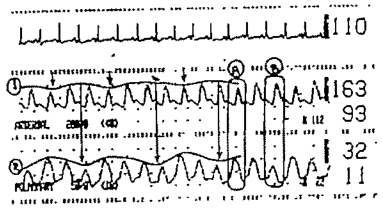
Department of Cardiac Anaesthesia and I.C.U, A H.E.P.A. G.H., Thessaloniki, Greece

Introduction: Early detection of cardiac tamponade (CT) may be of paramount importance to patients requiring any mode of positive - pressure ventilatory augmentation. Since the classic manifestations of CT may not be present at this stage and pulsus paradoxus occurs in other pathologic conditions as well, we undertook this study in order to examine the possibility of early detection of CT by comparing the waveforms of systemic and pulmonary artery pressures (SAP, PAP).

Methods: One hundred and twenty patients scheduled for cardiac surgery were included in the study, fullfilling the following criteria: SAP greater than 140 mmHg, CXray not indicative of CT, RAP within normal range, EF>45% and no sign of COPD. Complete haemodynamic profile was obtained by means of a Swan-Ganz catheter and an arterial line before administering any anaesthetic agent. A 3-channel recording of ECG, SAP and PAP was obtained and analyzed in each case by conventional planimetry and a computerized scanning - planimetry system, comparing corresponding beats of SAP and PAP. Since the area under a single pressure curve for a given beat is proportional to the stroke volume (SV) - the other factors remaining unchanged - , right and left SVs were compared in terms of relative values

Results - Discussion: Pulsus paradoxus of the PAP being out of phase to the corresponding puslus paradoxus of SAP was found in 4 patients (curves 1 and 2 in the tracing); this has been described by other investigators as a typical sign of CT.[1] Planimetric analysis showed the corresponding beats of SAP and PAP were inversely related in terms of SV values (e.g. A, B in the presented tracing). This can be explained by the presence of pericardial fluid inhibiting the smultaneous even fililing of the two ventricals (RV, LV) during a given moment of the respiratory cycle, systemic venous return to the RV being enhanced during inspiration, leaving diminished available pericardial space for the LV to dilate; the opposite occuring during expiration. The diagnosis was surgically confirmed (amounts of pericardial fluid: 250ml to 600ml) in all four cases.

Conclusion: We believe that analysis of the corresponding beats, as it is describedabove - even as a simple review of a recording (see tracing) - , of SAP and PAP waveforms may reveal the existence of occult CT before its classic manifestations supervene. The clinical implications of our method, applied in a general ICU population, remain to be seen.



---

[1] Shabetai R., Fowler N.O., Fenton J.C., Masangay M., Pulsus Paradoxus. J.Clin Invest. 44: 1882, 1965.

A.37

DETERMINANTS OF SYSTOLIC PRESSURE VARIATION IN PATIENTS VENTILATED AFTER VASCULAR SURGERY

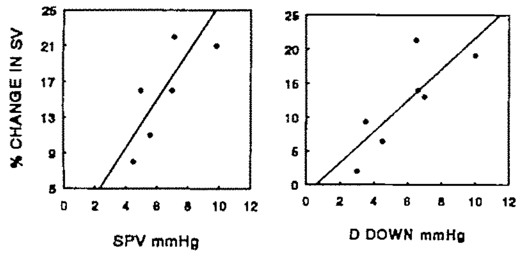
M. Beaussier, P. Coriat, M. Gosgnach, M. Portilla,
P. Kalfon, P. Viars
Department of Anesthesiology, CHU Pitié-Salpêtrière
University Paris VI, Paris, France

Perel et al. used systolic pressure variation (SPV) in response to positive pressure inspiration (PPI) as an estimate of stroke volume (SV) (1). These authors stated that an increased in SPV reflects a decrease in SV associated with hypovolemia. However, Denault et al (2) suggested that the decrease in SPV during PPI reflects withdrawal of the intrathoracic pressure effects on the arterial pressure. To determine the predominant determinant of SPV, we recorded simultaneously blood pressure (BP) and SV derived from beat to beat transoesophageal continuous wave Doppler trace.

Methods. We studied 7 patients who were sedated under mechanical ventilation following vascular surgery. Radial arterial pressure, airway pressure were simultaneously recorded. We measured SV at the following times : at the time of maximal and minimal systolic pressure (SP) during four mechanical breaths (difference in SP = SPV) ; during apnea and at the time of minimal SP during one cycle of mechanical breath (difference in SP = delta down).

Results. There exists a significant relationship between the decrease in SV and the magnitude of both SPV (r = 0.82) and delta down (D down) (r = 0.80).

	SPV	Delta down
Value in mmHg	7 ± 2	5.9 ± 2
% change in SV	17 ± 7	12 ± 7



Conclusion. The decrease in SP provoked by PPI reflects simultaneous decrease in SV. This suggests that a decrease in LV filling which limits ejection, rather than a fall in afterload, is responsible for PPI induced SPV. This finding confirms the interest of considering SPV to detect hypovolemia.

References. 1. Anesthesiology, 1987, 67, 498-502
2. Anesthesiology, 1992, 77, A129

A.38

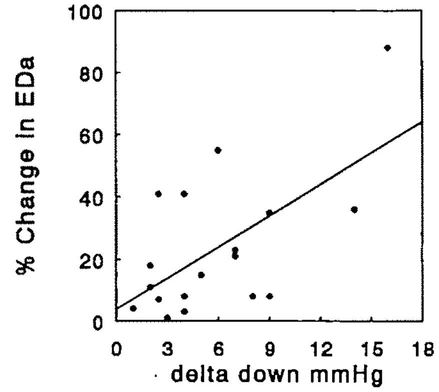
THE SYSTOLIC PRESSURE VARIATION PREDICTS RESPONSE TO VOLUME LOADING IN PATIENTS VENTILATED AFTER AORTIC SURGERY.

Pierre Coriat, Carlos Gomez, Georges Daas,
Azriel Perel, Pierre Viars.
Department of Anaesthesiology, CHU Pitié-Salpêtrière, Paris, France.

Background: As suggested by experimental (1) and clinical studies (2), the degree by which the systolic pressure (SP) decreases following a fixed tidal volume, termed delta down (ddown) is a sensitive indicator of hypovolemia. The aim of this study was to assess the ability of this parameter to predict LV function response to volume loading.

Patients and methods: We studied 18 patients who were sedated under mechanical ventilation following abdominal aortic surgery. Patients with LV ejection fraction < 35 %, PAOP > 18 mmHg or betablocker therapy were excluded from the study. The difference between the minimal SP during one cycle of mechanical breath and SP during apnea (ddown), TEE derived end diastolic area, and cardiac index were measured before and after volume loading with 500 ml of human albumin 4 %.

Results: The preinfusion ddown values showed a significant linear correlation to the increase in EDa (r=0.63) fig. and cardiac index (r=0.55) in response to volume loading. The higher the initial ddown the greater was the change in EDa and CI.



Conclusion: These findings indicate that in mechanically ventilated patients after vascular surgery, ddown is a useful means of cardiovascular assessment which provides reliable information concerning the LV response to volume loading.

References: (1) Anesthesiology, 67, 498-502, 1987.
(2) Anesthesiology, 73, A242, 1990.

A.39

INFLUENCE OF CHRONIC ANGIOTENSIN CONVERTING ENZYME INHIBITION ON SYSTOLIC PRESSURE VARIATION DURING ANESTHETIC INDUCTION

Louis Puybasset, Bart Oris, Pierre Coriat,
Marilyn Gosgnach, Pierre Viars.
Department of Anaesthesiology, CHU Pitié-Salpêtrière, Paris, France.

Background: By contrast to calcium channel blockers (CaB) Angiotensin converting enzyme inhibitors (ACEI) increase the lowering blood pressure effect of anesthetic induction (1). To better determine the mechanisms involved in this hypotensive response to induction we quantified systolic pressure variations (SPV) after induction of anesthesia in hypertensive (H.T.) patients chronically treated with ACEI. When SP decreased, SPV has be shown to be increased in case of low stroke volume associated with hypovolemia.

Methods: Blood pressure was recorded at induction in H.T. patients chronically treated with A.C.E.I. (n=15 group ACEI) or CaB (n=12 group CaB) and in 16 non treated non H.T. patients (group C). A standardized anesthetic technique was used in all these patients who underwent a vascular surgical procedure.

The S.P.V. and its delta down (ddown) component (difference between the value of minimal SP during one cycle of mechanical breath and SP during apnea) were determined after induction under mechanical ventilation when mean arterial pressure (MAP) was 20-30 % lower than the preoperative SP value. If MAP became lower than 30 % than its preoperative value phenylephrine was given.

Results: Are expressed as mean + SEM :

mmHg	C	CB.	ACEI
Preop MAP	95±2	100±4	93±2
SPV	6±0,6	6±0,8	8,5±0,7*
ddown	4±0,7	3,6±0,8	6,1±0,7*

ANOVA : * $p<0.005$ vs C and CB

Phenylephrine was needed in more pts in group ACEI (n=10) than in groups CaB(n=4) andC(n=2)p <0.05

Conclusion: The higher SPV due to by a mechanical breath in ACEI patients suggests that a decrease in the filling of the left ventricle which limits left ventricular ejection may contribute to the exaggerated hypotensive response to induction seen in this group.

Reference: Colson P. et al : Anesth. Analg., 74 : 805-812, 1992.

A.40

KETAMINE DOES NOT PREVENT HYPOTENSION CAUSED BY INDUCTION OF ANAESTHESIA WITH PROPOFOL IN ELDERLY PATIENTS

Dirk Blockmans, Jan Van Hemelrijck, Hugo Van Aken
Department of Anaesthesia
Katholieke Universiteit Leuven, Belgium

Background and goal of study:

The combination of propofol with a subanaesthetic dose of ketamine has been recommended, when haemodynamically stable anaesthesia is required[1,2]. However, this recommendation may not be valid for every patient. The goal of this study was to investigate if administration of ketamine could improve the haemodynamic stability during induction of anaesthesia with propofol in elderly, vascular patients.

Materials and methods:

Thirty consenting vascular surgery patients, older than 60 years of age, were randomy assigned to 1 of 3 treatment groups. Baseline blood pressure (BP) and heart rate (HR) were recorded before the administration of fentanyl, 2 µg/kg, and ketamine, 0 mg/kg (Group 1), 0.5 mg/kg (Group 2) or 1 mg/kg (Group 3), respectively. Three min later anaesthesia was induced with propofol, 1.5 mg/kg i.v. over 30 sec, and vecuronium, 0.1 mg/kg i.v.. Three min later the patients were intubated and ventilated with 100 % O_2. BP and HR were recorded before and during 10 min after the administration of propofol. A decrease in SAP below 80 mmHg before laryngoscopy or by more than 20 % compared to baseline after intubation, was treated with ephedrine or neosynephrine. The need for vasopressor treatment was compared. Results are expressed as mean values ± S.D. Anova was used to compare the age. HR and BP for all measurement times and the maximal decrease in BP in the 3 Groups were compared using Kruskal-Wallis statistic; $p<0.05$ was considered significant.

Results and discussion:

The age of the patients was 70 ± 10 y (Group 1), 68 ± 5 y (Group 2), and 70 ± 6 (Group 3) (n.s.). BP and HR profiles during the observation period were identical in all Groups. Vasopressor treatment was necessary in respectively 5/10 (Group 1), 4/10 (Group 2), and 7/10 (Group 3) patients. Mean arterial pressure decreased by 47 ± 11 % (Group 1), 35 ± 26 % (Group 2), and 46 ± 10 % (Group 3) (p = 0.284).

Conclusion:

In elderly, vascular patients, the administration of a subanaesthetic dose of ketamine before induction of anaesthesia with propofol does not prevent hypotension.

References:

1: Guit JBM et al. Ketamine as analgesic for total intravenous anaesthesia with propofol.
Anaesthesia 1991; 46:24-27.
2: Schüttler J et al. Optimierte Dosierungsstrategien für die totale intravenöse Anaesthesia mit Propofol und Ketamin. Anaesthesist 1191; 40: 199-204.

A.41

EFFECTS OF NITROUS OXIDE (N_2O) ON SYSTEMIC HAEMODYNAMICS, REGIONAL LEFT VENTRICULAR (LV) FUNCTION AND INCIDENCE OF MYOCARDIAL ISCHAEMIA (MI) IN VASCULAR SURGICAL PATIENTS WITH CORONARY ARTERY DISEASE (CAD)

Per Hohner, Christer Backman, George Diamond, Arnold Friedman, Sören Häggmark, Göran Johansson, Kjell Karp, Sebastian Reiz

Departments of Anaesthesia and Clinical Physiology, University of Umeå, Umeå, Sweden and Departments of Anaesthesia and Cardiology, Cedars Sinai Medical Centre, Los Angeles, Ca, USA.

Background & goal of study: N_2O has been shown to produce systolic wall motion abnormalities (SWMA) in dogs when added to opiates or isoflurane (1,2). It is clinical experience that N_2O may produce cardiac depression in patients with CAD. However, new SWMA-s caused by N_2O, indicating myocardial ischaemia (MI), have not been observed in such patients (3). This study examines the effects of N_2O on systemic haemodynamics, anterior LV function and incidence of MI in vascular surgical patients with CAD.

Materials & methods: 47 patients with CAD were randomly assigned to isoflurane-fentanyl anaesthesia with N_2O/O_2 vs air/O_2 (control). Systemic haemodynamics, 12-lead ECG and anterior LV wall motion by cardiokymography (CKG) were recorded at four intervals: before and during anaesthesia, then 10 and 30 minutes into surgery. Haemodynamics were controlled by changing anaesthetic dose, and, when insufficient, by iv nitroglycerine (NG) in case of LV failure (PCWP>18 mm Hg), or by iv phenylephrine (PE) in case of arterial hypotension.

Results & discussion: *(1)* More pre-induction MI was observed in the control group ($p=0.043$). *(2)* More N_2O patients ($p=0.031$) needed NG to control PCWP during surgery despite comparable anaesthetic dose, blood pressure and heart rate. *(3)* MI, defined as myocardial lactate production, new ST-segment depression >0.1mV in at least one lead, and/or new SWMA on CKG without elevated LV loading conditions, was more frequent in N_2O patients ($p=0.029$). *(4)* Postoperatively, MI by serial ECG was noted in more control patients ($p=0.038$) most likely because these patients had more severe CAD (more pre-induction MI). The incidence of postoperative myocardial infarction was comparable. We conclude that N_2O, which is known to have both sympathomimetic and cardiodepressive actions, produced overt cardiodepression in the face of sympathetic stimulation during surgery. Our study design does not allow us to conclude if MI was the consequence of increased wall stress or a contributor to the LV dysfunction. Postoperative MI was not a consequence of intraoperative events but did rather identify patients at higher risk for MI.

References: (1) Philbin D, et al: Anesthesiology 1985; 62:166 (2) Nathan H: Anesthesiology 1988; 68:407
(3) Slavik JR, et al: Anesth Analg 1988; 67:695.

A.42

EPIDURAL CLONIDINE AND MYOCARDIAL ISCHAEMIA AFTER ABDOMINAL AORTIC SURGERY

JP Fulgencio*, JM Rimaniol*, M Saada, P Catoire*,
F Bonnet***

**Departments of Anaesthesia, Hospitals H Mondor*,
94000 Créteil and Pitié Salpêtrière**, 75013 Paris, France**

Introduction: Clonidine (C) improves perioperative hemodynamic stability in high risk patients (1). C decreases arterial blood pressure and heart rate and may prevent the occurrence of myocardial ischemia (MI) but controversial data have been reported (2,3). We therefore conducted a blinded prospective study to assess if postoperative epidural C reduced MI in patients at risk.

Material and Methods: Forty five ASA 3 patients scheduled for abdominal aortic surgery were included in the study after informed consent and ethical committee approval. Surgery was performed under combined general and thoracic epidural anaesthesia. Postoperatively patients were randomly assigned to receive, in the recovery room, analgesia with a continuous epidural infusion of either fentanyl (0,4 mcg/kg/h) alone (F group) or fentanyl (0,4 mcg/kg/h) + C (0,3 mcg/kg/h) (F+C group). Patients were monitored during the first 24 postoperative hours with a ST segment analyser (Merlin^{R}, Hewlett-Packard), and pulmonary and radial artery catheters. MI was defined as a ST-segment decrease or increase over 1 mm from the base ligne, during at least 1 min. Hypotension was defined as a systolic arterial pressure < 90mmHg, hypertension as a systolic arterial pressure > 160mmHg and tachycardia as an increase in heart rate > 110bts/min. Hemodynamics events or MI were treated according to the judgment of the physician in charge of the patient, unaware of the analgesic regimen. Statistical analysis used Mann Withney U test and Fisher exact test. P<.O5 was considered significant.

Results: The 2 groups were comparable for demographics. 11 patients suffered of MI in the F group versus 6 in the F+C group (NS). The mean duration of MI was respectively 87±31min and 23±25min in groups F and F+C (NS). 21 and 11 episodes of MI occurred respectively in groups F and F+C in abscence of hemodynamic event while 16 episodes in both groups were associated with hemodynamic disturbances.

table 1: MI episodes according to hemodynamic events.

	hypotension	hypertension	tachycardia
F group	1	9	2
F+C group	0	1	3

($p<.05$)

Discussion: C may eventually blunt hypertension resulting from sympathetic activation from shivering or nociceptive stimulations in the recovery room and allows to avoid myocardial ischemia associated with increased oxygen demand, but the majority of MI events occurred without significant hemodynamic change. C may also be an appropriate treament of MI related to hypertension and tachycardia.

References: 1- Flacke J, Anesthesiology 1987;67:3-10. 2- Kent M, Anesthesiology 1990;73:A129. 3- Lipszyc M, Anesthesiology 1991;75:A93.

P25784
/

A.43

INFLUENCE OF POSITIVE PRESSURE VENTILATION ON MYOCARDIAL ISCHAEMIA AFTER ABDOMINAL AORTIC ANEURYSM REPAIR

D McCoy, M O'Connor, A Cunningham, R Dwyer

Department of Anaesthesia, Beaumont Hospital, Dublin 9, Ireland

Introduction: Ischaemic heart disease is common in patients presenting for abdominal aortic aneurysm repair and myocardial ischaemia is a major cause of postoperative morbidity and mortality[1,2]. Ventilatory support postoperatively might be useful by allowing heavy sedation and ensuring adequate oxygenation. We will present data comparing the incidence of postoperative myocardial ischaemia between patients who received postoperative positive pressure ventilation and patients who breathed spontaneously within 15 min of the end of abdominal aortic aneurysm resection. Preliminary data are described in this abstract.

Methods: Continuous ECG monitoring was instituted preoperatively to detect ischaemia in leads II and CM5 in 11 patients undergoing elective aortic aneurysm repair. After benzodiazepine premedication, anaesthesia was induced by thiopentone and fentanyl 2-5μg/kg and muscle relaxation provided by vecuronium. Anaesthesia was maintained by isoflurane in N_2O in O_2 and vecuronium administered as required. An epidural catheter was inserted before induction of anaesthesia; after release of the aortic cross clamp patients received an epidural infusion of bupivacaine 0.25% Four patients received positive pressure ventilation (mean duration 7 h) (Group I) and 7 patients were allowed to breathe spontaneously after antagonism of neuromuscular blockade and once adequate ventilatory function had returned (Group 2). The number and duration of episodes of significant S-T elevation or depression were compared between the two groups (Mann Whitney).

Results: Pre-operative Goldman scores and perioperative BP and HR were similar in both groups. There were no episodes of S-T depression in Group 1. In Group 2 the median number (quartiles) of episodes of S-T depression was 3 (0.75-3.75) ($p<0.05$) and of total duration of S-T depression was 3.9 (0.9-9.8) min ($p<0.05$).

Conclusion: Preliminary data suggest postoperative ventilatory support may decrease postoperative myocardial ischaemia after abdominal aortic aneurysm resection..

References: 1. Freeman MK et al: Abdominal aortic aneurysm and coronary artery disease: frequent companions but an uneasy relationship. J Vasc Surg 1990; 12: 73-77

2. Mangano DT: Perioperative cardiac morbidity. Anesthesiology 1990; 72: 153-184

A.44

FUNCTIONAL RECOVERY AFTER 24h PRESERVATION OF RABBIT HEARTS IN UNIVERSITY WISCONSIN SOLUTION

JL Fellahi, F Ouardali, S Mouren, J-F Baron, M Diaby, P Viars

Department of Anaesthesiology, Hôpital Pitié-Salpêtrière, Paris, France

Introduction. Complete myocardial functional recovery after 24 hours storage in the University Wisconsin Solution (UWS) has been demonstrated. However, two different groups of hearts with and without ischemia were used in these studies. Our approach was to compare the myocardial performance of isolated blood-perfused rabbit hearts before and after 24 h hypothermic preservation in UWS.

Method. Reconstituted blood with red blood cells and modified Krebs-Henseleit buffer was oxygenated and equilibrated to achieve normal acid-base balance. After aortic canulation, the coronary network was perfused at constant perfusion pressure of 80mmHg using the langendorff technique. The speed of the coronary pump reflects the coronary blood flow (CBF). An atrial pacing maintained a constant heart rate of 120 b/min. A cannulated fluid-filled balloon was inserted in the left ventricule(LV) to maintain constant LV volume and to monitor the LV pressures. Maximal positive and negative LV pressure derivatives were derived and reflected respectively myocardial contractility (dP/dt max) and relaxation (dP/dt min). Baseline measurements were obtained one hour after aortic canulation (Control). Cardiac arrest was obtained by infusion of cooled UWS and the heart was stored in 4°C UWS. After 24 hours preservation, reperfusion was performed for 2 hours. Five additionnal hearts stored for one hour were used as control group to determine the effects of our protocol on functional recovery. Arterial and venous samples were withdrawn before the cardiac arrest and at 60,90,and 120 minutes reperfusion. The statistical significance was determined by ANOVA.

Results. Ten hearts were used for the statistical analysis. Hemoglobin value did not vary during the study. When compared to control, CBF was lower at 60 minutes reperfusion and unchanged at 90 and 120 min reperfusion. Decreased dP/dt max and dP/dt min were observed during the reperfusion period. The significant decrease in myocardial oxygen consumption (MvO2) during reperfusion was associated with a lactate production. A 10% impairment of dP/dt max was observed in the 5 control hearts.

Discussion. In this study, 56% functional recovery is observed after 24 h storage in UWS. This impairment in myocardial performance is related to an imbalance between oxygen supply and demand as demonstrated by the decrease in MvO2 and the lactate production.

	Control	R 60	R 90	R 120
Hemoglobin (g/100 ml)	9.06±0.26	8.81±0.42	8.98±0.35	9.01±0.53
DCo ($ml.mn^{-1}.g^{-1}$)	2.42±0.24	1.27±0.26*	1.89±0.41	1.75±0.42
dP/dtmax ($mmHg.s^{-1}$)	2395±174	882±193*	1245±247*	1341±295*
dP/dtmin ($mmHg.s^{-1}$)	1705±128	592±153*	850±201*	935±235*
MVO2 ($ml.mn^{-1}.100g^{-1}$)	7.56±0.66	3.06±0.6*	4.16±1.36*	4.99±1.35*
Lactates AV Difference	0.43±0.1	-0.77±0.5	-0.83±0.5	

* $p < 0.05$

A.45

EFFECTS OF HYPERTONIC SALINE ON CORONARY BLOOD FLOW AND MYOCARDIAL PERFORMANCE OF A BLOOD-PERFUSED, ISOLATED RABBIT HEART

S Delayance, G Mion, S Mouren, J-F Baron, M Diaby, P Viars

Department of Anaesthesiology, Hôpital Pitié-Salpêtrière, Paris, France

Introduction. Hypertonic saline is proposed for treatment of hemorragic shock. Its effects on volemia and peripheral vessels are demonstrated whereas its myocardial effects remain debated. Indeed, the observed increase in myocardial performance could be mediated through direct or indirect mecanisms. In order to determine the effect of hypertonic saline on the coronary blood flow and myocardial performance, increasing sodium concentrations ([Na]) were infused to isolated blood-perfused rabbit hearts. The studied concentrations included the [Na] observed in vivo after hypertonic saline infusion.

Method. Reconstituted blood with red blood cells and modified Krebs-Henseleit buffer was oxygenated and equilibrated to achieve normal acid-base balance. After aortic canulation, the coronary network was perfused at constant perfusion pressure of 80mmHg using the langendorff technique. The speed of the coronary pump reflects the coronary blood flow (CBF). An atrial pacing maintained a constant heart rate of 100 b/min A cannulated fluid-filled balloon was inserted in the left ventricule(LV) to maintain constant LV volume and to monitor the LV pressures. Maximal positive and negative LV pressure derivatives were derived and reflected respectively myocardial contractility (dP/dt max) and relaxation (dP/dt min). Blood perfusates with increasing [Na] from Na 140mM/l (Control) to 180 mM/l were infused. Between each infusion, the control perfusate was infused and time was allowed to return to baseline values. Arterial and venous samples were withdrawn for blood gas analysis before and after each hypertonic infusion. Statistical significance was determined by ANOVA.

Results. CBF increase significantly with [Na] higher than 140 mM/l. dP/dt max and dP/dt min increased with all the studied [Na]. dP/dt max reached its peak value for Na 160mM/l. The myocardial oxygen consumption (MvO2) increased with all the studied [Na].

Conclusions. In this study, a coronary vasodilation is demonstrated in the range of [Na] observed in vivo after hypertonic saline. This effect is related both to the perfusate osmolarity and the increase in MvO2. The increase in myocardial contractility and relaxation reflect the direct effects of the hypertonic saline on the myocardial fibers.

	Na 140	Na 150	Na 160	Na 170	Na 180
CBF (ml/min/g)	1.55±0.66	2 27±0.82 **	1.98±0.87**	2.13±0.88**	2.32±0.97**
dP/dt max (mmHg/s)	1861±468	2133±447*	2355±567**	2370±581**	2394±598**
dP/dt min (mmHg/s)	1166±361	1383±401**	1422±499**	1363±485**	1333±504**
MvO2 (ml/min/100g)	5.2±1.9	6.7±2.5**	6 2±2*	6.9±2.4**	7.3±2.6**

* $p < 0.05$; ** $p < 0.01$

A.46

PRE- AND INTRAOPERATIVE PREVENTION BY β-BLOCKERS, PROPRANOLOL AND ESMOLOL, OF ISCHAEMIA-INDUCED VENTRICULAR FIBRILLATION

M Freysz, Q Timour, L Bertrix, J Loufoua, G Faucon

Med Pharmacol Dept, Cl Bernard University, Lyon, France

It is common to use ß-blockers in subjects with angina pectoris or even acute myocardial infarction to improve tolerance to ischemia by reducing mechanical energy expenditure of the heart, especially in the case of an underlying excess of sympathetic activity. The balance between cardiac energetic metabolism and coronary blood flow is maintained below the threshold triggering serious disorders including ventricular fibrillation, the most dramatic of these disorders in patients with coronary disease. The goal of this study was to better define the benefit which might be obtained from ß-blockers using a pig model.

The study was conducted in domestic pigs premedicated with i.m. droperidol and anesthetized with i.v. flunitrazepam and chloralose, whose core temperature was kept constant. After left thoracotomy, the left anterior descending coronary artery was dissected a few millimeters below its origin and a snare passed around it to produce complete occlusion. Occlusion was maintained until the onset of fibrillation in order to measure time to fibrillation (TF), which is altered by factors or drugs which change the vulnerability to fibrillation for a given rate. Additionally, two monophasic action potentials (MAPs) were continuously recorded, one in the area transiently subjected to ischemia and one in a non-ischemic area.

In group 1 ($n = 20$), the TF measurement was perfomed during atrial pacing at a rate just above the sinus rate. As ß-blockers are chiefly used to counteract excessive adrenergic influence, the animals received an i.v. infusion of isoproterenol 0.25 μg/kg/min and, in addition, 15 min after the start of isoproterenol infusion, propranolol 0.05 mg/kg ($n = 8$) or esmolol 1.00 mg/kg ($n = 6$). In group 2 ($n = 12$), propranolol ($n = 8$) or esmolol ($n = 4$) were administered in the absence of isoproterenol, but under pacing at a constant high rate, 180 bpm.

In group 1, TF was considerably reduced by isoproterenol (263 ± 59 to 69 ± 30 s), then came back to its control values 5 and 20 min (235 ± 85 s) ($P < 0.05$) after the injection of propranolol. The restoration of TF was less complete with esmolol (184 ± 68 s) ($P < 0.05$) at 5 min and not as long lasting, since the difference with control values ceased being significant at 20 min. This time course of TF was related to sinus rate, slowed down by propranolol (161 ± 17 to 103 ± 11 bpm) ($P < 0.05$), as well as by esmolol (156 ± 15 to 112 ± 16 bpm) ($P < 0.05$). Bradycardia also was responsible for the widening of MAP by 30 or 40 % with both drugs, in the ventricle not subjected to ischemia. However, during the ischemic periods, MAP duration underwent the same reduction as usual. In group 2, in the absence of any variation in heart rate (180 bpm) and MAP duration (220 ms), TF (near 100 s) did not appear to be significantly influenced by the administration fo propranolol or esmolol.

We conclude that propranolol or esmolol are capable of preventing ischemic ventricular fibrillation by controlling tachycardia of sympathetic origin. The effects of propranolol are longer and of interest preoperatively. The effects of esmolol do not exceed 5 to 10 min and are more suitable for avoiding an intraoperative tachycardia episode. However, the protective action does not result from a direct ventricular effect, but from the influence on heart rate, as the prolongation of TF is always associated with a fall in heart rate and dissappears under pacing at constant rate. In addition, variations in pacing rate similar to those in sinus rate due to isoproterenol and ß-blockers provide the same change in TF.

A.47

ENDOCARDIAL ENDOTHELIUM MODULATES IN VIVO LEFT VENTRICULAR PERFORMANCE

Stefan G. De Hert *, Thierry C. Gillebert, Dirk L. Brutsaert

Department of Anaesthesia (*), Department of Physiology
University of Antwerp, Antwerp, Belgium

Background: Selective damage of endocardial endothelium (EE) modulates myocardial performance in isolated cardiac muscle (1, 2) and in the intact ejecting ventricle (3). We analyzed the relevance of this phenomenon under different experimental conditions.

Methods: The dogs were instrumented with LV micromanometer, left atrial pressure, LV segment length gauges and right atrial pacing. EE function was transiently impaired with an ultrasound (UL) probe ($P = 25W$; $f = 0.9$ Mhz) in the LV cavity (3). The effects of UL were evaluated under different conditions of LV volume, contractile state and after mild selective alpha$_1$-adrenergic stimulation.

Results: In protocol A ($n = 10$), LV volume was altered with caval vein occlusion and intravenous dextran infusion. The UL probe was activated at low, mid and high LV end-diastolic pressure (EDP). Effects of UL were less pronounced at higher EDP ($p < 0.001$). In protocol B ($n = 7$), LV inotropic state was altered by slow intravenous infusion of low dose calcium. The UL probe was activated before and after calcium. Effects of UL were less pronounced after calcium ($p < 0.001$). In protocol C ($n = 7$), effects of UL were evaluated at baseline and after mild selective alpha$_1$-adrenergic stimulation (propranolol + phenylephrine (PE)). Effects of UL were similar at baseline and after propranolol but increased after PE.

Conclusion: UL modulated LV performance by transiently impairing EE function. These effects were more important at low volume and at lower calcium and under mild selective alpha$_1$-adrenergic stimulation.

References:

1. Brutsaert DL, Meulemans AL et al. Effects of damaging the endocarial surface on the mechanical performance of isolated cardiac muscle. Circ Res 1988; 62: 358-366.
2. Andries LJ, Meulemans AL et al. Ultrasound as a novel method for selective damage of the endocardial endothelium. Am J Physiol 1991; 261: H1636-H1642.
3. Gillebert TC, De Hert SG et al. Intracavitary ultrasound impairs left ventricular performance: presumed role of endocardial endothelium. Am J Physiol 1992; 263: H857-H865.

A.48

DOES CAPTOPRIL MODIFY THE ARTERIAL RESPONSE TO VASOPRESSOR SUBSTANCES ?

Eric Le Pelley*, Thierry Chataigneau**, Jean-Pierre Richer***, Robert Tricoche**, Jacques Fusciardi*

(*)Departement of anesthesiology,(**)Laboratory of animal physiology, (***)GRTMV, University of Poitiers, Poitiers, France.

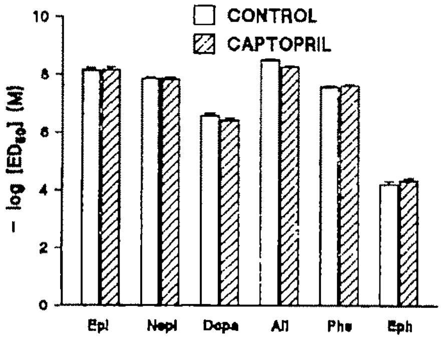
Background and goal of study: Captopril, an angiotensin-converting enzyme inhibitor, has a vasodilatory activity which depends on the renin-angiotensin system. It has also a direct endothelium-dependent vasodilatating action. During the induction of anesthesia in patients treated by Captopril, hypotension is often observed. The purpose of this study was to investigate the effect of Captopril on the vascular response to vasopressor substances in swine femoral artery rings.

Materiels and methods: Vascular rings (2,5mm in length and 2mm in diameter) were suspended in tissue baths and optimal tension determined. The integrity of the endothelium of each ring was assessed by the Acetylcholine (10^{-7}M)-induced reversion of a Kcl (20mM)-increased contraction. Then the rings were repeatedly washed, and the tension returned to the initial level. Renin (1mUI/ml) was added in all baths, and after 45 min. either captopril (100 microM) or water (control) were added. After 15 min., the rings were constricted with increasing doses(10^{-10} to 10^{-3} M) of Epinephrine, Norepinephrine, Phenylephrine, Ephedrine, Dopamine or Angiotensin II.

Results and discussion: The concentration-response curves for each vasopressor substances are the same with or without Captopril. As shown by the figure , ED_{50} are the same with or without Captopril.

Conclusion: Therefore Captopril(100 microM) doesn't modify the constrictive substances-induced vascular response of swine femoral arteries.

Reference: Kikta D, Fregly M: Effect of in vitro administration of captopril on vascular reactivity of rat aorta.Hypertension 1982;4:118-124.



A.49

DOES EXOGENOUS DOPAMINE REVERSE CARDIOVASCULAR DEPRESSION INDUCED BY ISOFLURANE DURING THORACIC EPIDURAL BLOCKADE?

C. Raner MD, B. Biber MD, J. Lundberg MD,
J. Martner MD, Ola Winsö MD.

Dept. of Anesthesiology, University of Gothenburg,
Östra Hospital, Gothenburg, S-416 85 Sweden

Background and aim: Cardiovascular support by exogenous adrenergic receptor agonists is clinical routine to counter the depressor responses during epidural or spinal sympathetic blockade. Cardiovascular depression by inhalational agents is on the other hand usually managed by decreasing the dose of the anesthetic agent, which also causes alterations in anesthetic depth. This constitutes a significant risk for awareness. The aim of this study was to evaluate the cardiovascular effects of exogenous dopamine (DA) during isoflurane (ISO) anesthesia, as combined with a thoracic epidural blockade (TEA).

Materials and methods: DA (10 and 20 $\mu g \cdot kg^{-1} \cdot min^{-1}$) was infused in mechanically ventilated dogs during chloralose anesthesia before and during the combined administration of ISO (1.4% in 50 % O_2;1.0 MAC) and TEA (extension of sympathetic blockade including Th_4). Heart rate (HR), mean aortic pressure (MAP), mean pulmonary artery pressure (MPAP), pulmonary artery occlusion pressure (PAOP), cardiac output (CO; thermodilution), left ventricular end-diastolic pressure (LVEDP) and the maximum rate of change of left ventricular pressure (LV dP/dt) were measured.

Systemic vascular resistance (SVR) was calculated. Statistical significance was assessed by analysis of variance (ANOVA) and least square means.

Results and discussion:

Prior to ISO-TEA, DA increased MAP, CO and LV dP/dt. ISO-TEA decreased HR, MAP, CO and LV dP/dt, while SVR, MPAP and PAOP were not changed.

During ISO-TEA, the DA-induced increases in MAP and SVR were significantly more pronounced than prior to ISO-TEA. At the dose 10 $\mu g \, kg^{-1} min^{-1}$, DA restored MAP, CO, and LV dP/dt to levels found before ISO-TEA. At the DA dose 20 $\mu g \cdot kg^{-1} \cdot min^{-1}$, HR was restored to and MAP (39%), LVdP/dt (119%), SVR (28%) and MPAP (70%) were increased above levels prior to ISO-TEA.

Conclusion: Exogenous DA effectively and dose-dependently counters cardiovascular depression induced by the anesthetic technique of combining ISO and TEA. The pressor and systemic vasoconstrictor actions of DA are indicated to be potentiated by this combined anesthetic approach.

A.50

LOCAL VERSUS NEUROGENIC VASODILATOR EFFECTS OF DESFLURANE AND ISOFLURANE IN THE SMALL INTESTINE

H.Sundeman, B.Biber, O.Winsö, J.Martner,
C.Raner.

Dept. of Anesthesiology, University of Gothenburg,
Östra Hospital, S-416 85 Gothenburg, Sweden.

Background and aim: The general cardiovascular profile of action of the new volatile anesthetic desflurane (D) is similar to that of isoflurane (I), although data on regional hemodynamic effects of D are sparse (1). The aim was to evaluate vasodilator mechanisms of D and I in the intestinal vasculature.
Materials and methods: D or I was injected into a closed anesthesia circuit for cats (n=11) during basal chloralose anesthesia and controlled normoventilation. Hemodynamic measurements included heart rate (HR), mean arterial pressure (MAP) and small intestinal blood flow (IBF; optical drop flowmetry). Intestinal vascular resistance (IVR) was derived.
To avoid changes in local vascular tone related to transluminal pressure alterations, intestinal perfusion pressure (IPP) was controlled and kept constant by a variable aortic clamp. Measurements were made at 50 mmHg IPP during control and during the randomized subsequential administration of D (3.5% and 7.0%) and I (0.8% and 1.6%), i.e. doses corresponding to 0.5 MAC and 1.0 MAC respectively.
The registration sequence was repeated after intestinal postganglionic denervation.
Results: D and I dose-dependently decreased MAP. At each MAC level, this depressor response was more pronounced for D than for I. In the *innervated* intestine, D and I both dose-dependently decreased IVR. At the highest dose of each agent, D decreased IVR more than I. Denervation of the intestine significantly reduced base-line vascular resistance.
In the *denervated* intestine, a less pronounced vasodilation, as compared to the innervated state, was produced by both D and I. Both agents produced similar degrees of vasodilation. Also, the vascular relaxation was not dependent on the given dose of either agent.
Conclusion: D and I are both dilators of the intact intestinal vasculature, although 7,0% D seems more powerful than 1,6% I. In the denervated intestine, less powerful intestinal vasodilation was observed, suggesting that actions mediated through remote nervous vascular control mechanisms are significant for the vascular intestinal effects of both D and I. Denervation data indicate that, for the vasculature in the intestine, local control mechanisms have a different dose-response relationship than remote control mechanisms. This applies to both D and I.
Reference: 1. Anesthesiology 1991;74:568-74.

A.51

A COMPARISON BETWEEN VARIOUS HEMODYNAMIC PARAMETERS REFLECTING PRELOAD DURING GRADED HEMORRHAGE IN VENTILATED DOGS.

Sergei Preisman, Alexander Shneider, Ulrich Pfeiffer,
Azriel Perel
Department of Anesthesiology, Sheba Medical Center,
[Sackler School of Medicine, Tel Aviv University]
Tel Hashomer, Israel 52621, and Pulsion Medizintechnik,
Munich, Germany.

Background and goal of study: The estimation of the volume status is a major part of monitoring critically Ill patients. Two new parameters for preload assessment have been recently introduced:1. The dDOWN, which is the difference between the minimal systolic blood pressure (SBP) during one mechanical breath and the SBP during a short apnea(1). 2. The intrathoracic blood volume (ITBV),which is measured by a double indicator (temperature and dye) dilution technique (2). We have compared the correlation of these two parameters to other hemodynamic parameters which are used conventionally for volume status assessment.
Materials and methods: Eight dogs were anesthetized, ventilated and bled by 10% ,20% and 30% of their blood volume. The dogs were then retransfused (RET) and loaded with 10 ml/kg of plasma expander (LOAD). Central venous (CVP) and wedge (WP) pressures were measured at each point, in addition to cardiac index (CI) and ITBV. The dDOWN was measured by a computer program and expressed in absolute values (mmHg), or as % of the SBP during apnea (% dDOWN).
Results and discussion: The results of the study are presented in the following table (mean ± SD):

	baseline	10%	20%	30%	RET	LOAD
dDOWN (mmHg)	7.0 ±4.3	9.3* ±3.1	11.2* ±3.1	11.9 ±2.9	7.8* ±2.3	4.7* ±2.7
%dDOWN (%)	5.6 ±3.2	8.1* ±2.9	9.8* ±3.2	11.1 ±3.8	5.4* ±1.9	3.0* ±1.8
ITBV (ml/kg)	29.7 ±4.5	26.8* ±5.3	23.9* ±4.3	23.1 ±3.0	30.8* ±4.7	35.2* ±4.9
CI (ml/kg/ min)	159 ±44	128* ±43	109* ±37	96* ±29	170* ±48	195* ±59
SVI (ml/kg)	1.3 ±.4	1.0* ±.3	0.8* ±.3	0.7* ±.2	1.2* ±.4	1.4* ±.4
CVP (mmHg)	5.5 ±.9	4.6 ±1.3	3.6 ±1.4	3.1 ±1.7	5.9* ±1.8	7.4 ±2.2
WP (mmHg)	8.0 ±.8	6.4* ±.9	5.4 ±1.4	5.1 ±1.2	9.1* ±2.2	9.9 ±2.7

* $p < .05$ in comparison to previous value

The following r values were found for correlation with the degree of volume change: dDOWN -0.64; %dDOWN -0.76; CI 0.63; SVI 0.63; ITBV 0.70; WP 0.72; CVP 0.67. There were signi-ficant correlations between ITBV and SVI (r=0.87), ITBV and dDOWN (r=-0.70), ITBV and %dDOWN (r=-0.77).
Conclusions: In the experimental setup of graded hemorrhage, the ITBV,dDOWN and %dDOWN reflect the volume status with the approximate same accuracy as commonly used hemodynamic parameters. This similarity may however change in other circumstances, such as heart failure. The dDOWN, being the least invasive of all variables measured in this study, is a clinically useful parameter for detecting changes in volume status.
References: 1.Perel A, et al.Anesthesiology,67:498,1987. 2.Hedenstierna G. Intesive Care Med.18:137,1992.

A.52

INFLUENCE OF CERVICOTHORACIC EPIDURAL ANAESTHESIA (C-TEA) ON LEFT VENTRICULAR (LV) CONTRACTILITY - AN EXPERIMENTAL STUDY IN PIGS WITH AUTONOMOUS BLOCKADE.

Sebastian Reiz, Elisabet Nyström, Mehmet Tugrul, Sören Häggmark, Göran Johansson.

Department of Cardiothoracic Anaesthesia & Surgery, University of Umeå, Umeå, Sweden.

Background & goal of study: Electrophysiologic studies have shown that C-TEA produces effects on the heart similar and additive to those of beta-blockers (1). C-TEA has been shown to reduce infarct size in dogs (2) and alleviate unstable angina in humans (3). Dilation of stenotic coronary segments has been suggested as an important mechanism by which myocardial ischaemia is alleviated in patients (4). No experimental or clinical studies have, however, documented the effects of C-TEA on LV contractility, the most important contributor to myocardial oxygen requirements. The objective of this study was to investigate the influence of C-TEA on LV end-systolic pressure-volume relationships (ESPVR) and other indices of LV contractilitiy.

Materials & methods: Six female pigs were subjected to continuous pentobarbitone anaesthesia and autonomous blockade with hexamethonium and atropine. Atrial pasing was used to maintain heart rate constant. A conductance catheter was placed in the LV for derivation of LV volume (5) and pressure. Aortic and pulmonary arterial pressures, cardiac output and a V5 ECG were recorded. ESPVR was derived over 15 sec using inferior vena cava balloon occlusion. After baseline measurements, 5 ml 0.5% bupivacaine mixed with 2 ml dye were injected epidurally at the T2 level under fluoroscopy. Repeated ESPVR-s were obtained 15, 30 and 45 min after C-TEA.

Results & discussion: C-TEA (C3 to T6) did not decrease aortic pressure. The slope of ESPVR decreased from 2.3 ± 0.2 (mean±SD) at control to 1.6 ± 0.2 at 15 min, 1.4 ± 0.3 at 30 min and 1.5 ± 0.3 at 45 min (all $p<0.05$ compared to control). LV stroke work and LVdP/dTmax vs LV end-diastolic volume also decreased significantly. The results demonstrate that C-TEA decreased LV contractility by an average 39%. This is considerably more than could be expected from systemic haemodynamic measurements and could explain a major part of the beneficial effects of C-TEA on experimental and human myocardial ischaemia.

References: 1. Hotvedt R, et al: Cardiovascular Research 1983, 17:259. 2. Davis RF, et al: Anaesth Analg 1986, 65:711. 3. Blomberg S, et al: Anesth Analg 1989, 69:558. 4. Blomberg S, et al: Anesthesiology 1990, 73:840. 5. Baan J, et al: Circulation 1984, 70:812.

A.53

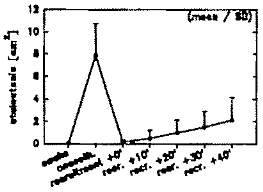
RECRUITMENT OF ATELECTASIS DURING GENERAL ANAESTHESIA: A CT-STUDY

Hans Ulrich Rothen, Bengt Sporre, Greta Engberg,
Göran Wegenius, Göran Hedenstierna
Institutes for Clinical Physiology / Anaesthesiology
and Intensive Care / Radiology,
Akademiska Sjukhuset, Uppsala, Sweden

Introduction: *Hypoxemia* during general anaesthesia is still a frequent finding [1]. The formation of *atelectasis* is one of the reasons for an altered gas exchange. Atelectasis is found in about 90% of all adult patients and there is a correlation between pulmonary shunt and atelectasis [2].

Question: Is it possible to reduce the amount of atelectasis by deep inflations of the lungs and do the recruited parts remain areated over time?

Material and Methods: Consecutive sample of lung healthy adults, scheduled for elective surgery. Intravenous anaesthesia (Propofol, Fentanyl, Pancuronium), controlled ventilation, end-tidal CO_2 4.0 kPa, FiO_2 4.0. Recruitment manoeuvre: Inflation of the lungs, three times up to an airway-pressure (P_{aw}) of 30 mbar and finally once up to P_{aw}=40 mbar. Every inflation was held for 15 seconds. Between these inflations, the lungs were ventilated conventionally for 2-3 minutes. Atelectasis was estimated as previously described [2]: For each analysis, a computed x-ray tomography was performed at end-expiration in a transverse plane 1 cm above the top of the right diaphragm. The atelectasis was calculated as amount of the dense areas (+100 to -100 Hounsfield units).



Atelectasis before and after Recruitment Manoeuvre

Results and Discussion: Up to now, 5 patients have been studied. Age (mean/range): 47/40-59 years, body weight (mean/range): 79/64-90 kg. Mean amount of atelectasis awake 0 cm², after induction of anaesthesia 7.9 cm². For changes after the recruitment manoeuvre, see figure. $P_{A-a}O2$ [kPa]: awake 1.4, anaesthesia 14.8; 5, 10, 20 and 40 minutes after recruitment manoeuvre: 10.7, 11.0, 11.9 and 11.9 respectively.

In previous studies, a reduction of atelectasis by PEEP has been found [3]. In contrast to our findings, there was however an immediate reappearance of the atelectasis after cessation of PEEP.

Conclusion: During general anaesthesia, atelectasis may be recruited by deep inflations of the lungs and the recruited lung-tissue remains areated in parts for at least 40 minutes. The mechanisms responsible for atelectasis formation and the prolonged effect of the recruitment manoeuvre remain to be elucidated.

References:
1 Moller J T, et al: Hypoxemia during anaesthesia - an observer study. Br J Anaesth 1991, 66:437-444.
2 Gunnarsson L, et al: Influence of age on atelectasis formation and gas exchange impairment during general anesthesia. Br J Anaesth 1991, 66:423-432.
3 Tokics L, et al: Lung collapse and gas exchange during general anesthesia: effect of spontaneous breathing, muscle paralysis, and positive end-expiratory pressure. Anesthesiology 1987, 66:157-167.

A.54

THE RESPIRATORY COMPLIANCE IN NORMAL AND OBESE SUBJECTS DURING ANAESTHESIA

Davide Mulazzi, Emiliana Calappi, Massimo Croci

Servizio di Anestesia e Rianimazione, IRCCS Ospedale Maggiore, Milano, Italy

This study evaluates the effect of position change (supine vs prone) on the respiratory system compliance (Crs) in normal and obese patients during general anaesthesia.

Material and methods : We studied 18 normal and 6 obese (BMI ≥ 24) patients undergoing general inhalation anaesthesia for spinal cord surgery; all were mechanically ventilated (Servoventilator 900 C, Siemens). In supine position the airway pressure was recorded during an inspiratory hold (3 s) at TV 8 ml/Kg to compute TSLC; in 14 normal and 4 obese patients this manoeuvre was repeated at higher TVs to obtain the slope of the V-P curve (Cinf). After prone positioning (assuring free abdomen mouvements with upper chest and pelvic supports), we repeated all measurements.

Results and discussion : The results are reported in the table. In supine position TSLC was lower in obese than in normal patients ($p < 0.05$) while in prone position no difference was observed, due to both a TSLC reduction in normal patients and an increase in the obese ones. In all patients Cinf was higher than TSLC, suggesting an upward inflection point in the lower part of the V-P curve. No Cinf differences were observed between normal and obese patients both in prone and supine position.

Our result confirm that in anaesthetized obese patients fat and abdomen enchroaches on the respiratory system, shifting V-P curve below normal (1); in prone position this mass loading effect is lost, increasing TSLC to normal values for a subject receiving general anaesthesia in prone position.

	SUPINE	PRONE
TSLC (ml/cmH2O)		
Normal	49.9 ± 12.1	44.0 ± 10.8*
Obese	38.4 ± 6.5°	43.2 ± 6.4*
Cinf		
Normal	77.4 ± 12.2	66.5 ± 12.2*
Obese	65.9 ± 7.9	59.0 ± 3.1

° $p < 0.01$ supine vs prone
*$p < 0.05$ normal vs obese

Reference: Sharp J.T et al. : Effect of mass loading the respiratory system in man. J. Appl. Physiol. 1964,

A.55

CONTINUOUS SPIROMETRY: AN AID IN THE INTRAOPERATIVE RESPIRATORY MONITORING-CASE REPORTS

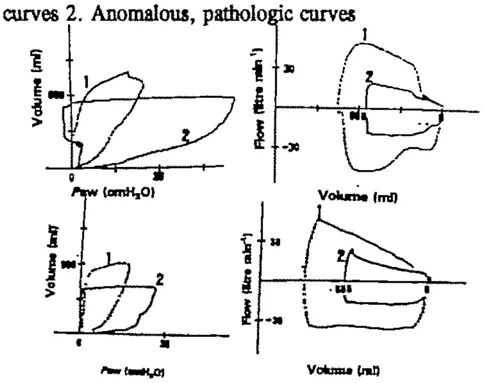
G.Bardoczky MD, E.Engelman MD.
A.d'Hollander MD,PhD.
Dept of Anesthesiology, Erasme University Hospital
808. Route de Lennik
1070 Brussels, Belgium

The Ultima SV™ respiratory monitor (Datex Instr. Helsinki, Finland) is used for routine intraoperative monitoring in our hospital. Spirometry is an integral part of the monitor equipped with a bi-directional flow sensor, which provides continuous measurements of inspiratory and expiratory flows, pressures and volumes(1). PV and FV loops are drawn from these parameters, displayed and updated continuously. Changes in compliance and airway resistance, or the expiratory flow characteristics of the whole respiratory system (lung, thorax, endotracheal tube) are depicted by the changing form of each loop. Compromised airway patency can alter the shape of the PV and FV curves in a particular way, which may be helpful to detect the origin of the problem.

We would like to present several cases, where the configuration of the curves was altered due to airway related complications.

Figure 1.

Pressure-volume (left panel) and flow-volume (right panel) curves recorded in a patient with kinked endotracheal tube (upper two curves) and in a patient with severe bronchoconstriction (lower two curves). 1.Baseline, normal curves 2. Anomalous, pathologic curves



COMMENTS

Both cases depicted here were associated with increased inspiratory pressures during mechanical ventilation. The right and downward shifted PV curve with enlarged area may illustrate this increased airway resistance. FV loops provide further information. The kinked endotracheal tube result both inspiratory and expiratory obstruction and equally diminished inspiratory and expiratory flow. Bronchoconstriction is characterized by diminished expiratory flow, and the convex configuration of the expiratory limb reveals uneven lung emptying.Continuous monitoring of PV and FV loops may be useful addition to detect compromised airway patency.

Ref.: 1. J Clin Monit 1992:8:251-252

A.56

INFLUENCE OF POSTURE ON THE RESPIRATORY MECHANICS DURING ANESTHESIA

E.Engelman MD, G.Bardoczky MD.
A.d'Hollander MD.

Dept of Anesthesiology,Erasme University Hospital
808 Route de Lennik,1070 Brussels, Belgium

Changes in posture may influence the ventilation of the anesthetized, paralyzed subject(1). This study was carried out to observe the influence of the head-up and head-down positions on the ventilatory variables evaluated with a new flow sensor.

METHODS.Fourteen consenting,healthy women were anesthetized with continuous infusion of propofol.Their lungs were ventilated with a 100 ml/kg/min constant volume. A new, two-sided, pressure based flow sensor (2) measures flow, pressure at the endotracheal tube and integrates volume and other ventilatory data from these values. Pressure-volume and flow-volume curves are displayed continuously. Data were recorded after induction of anesthesia in the horizontal position; in the 25° head up, and in the 25° head down position. Data were compared with the Friedman's two way analysis of variance, $P < 0.05$ was significant.

RESULTS: In the head up position, no significant changes of the ventilatory parameters occured.The pressure-volume characteristics of the respiratory system did not change significantly (fig.1). Head down tilting of the patients resulted in significant increase in peak inspiratory (19.5±4 vs 16.9±4 cmH2O in horizontal), and plateau (15.2±4 vs 13±4 cmH2O in the horizontal) pressures, decrease in the compliance (49.4±11 vs 60.4±15 ml/ cmH2O).The pressure - volume curve shifted to the right, its slope was diminished. There was a heightening of the peak expiratory flow and an increased convexity of the terminal expiratory part of the flow-volume curve (fig.1).

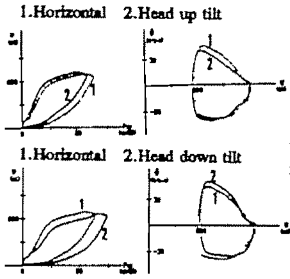


Figure 1.
Pressure-volume (left panel) flow-volume (right panel) curves

COMMENTS: When the diaphragm is paralyzed, its move is induced by the airway pressure, and opposed by the weight of the abdominal content. In the head up position, the visceral weight shifts away from the diaphragm- no ventilatory change will occur. In the head down position, the abdominal contents gravitate toward the diaphragm, the compliance of respiratory system decreased, and higher inflating pressure is required to achieve a given lung volume.This increased intrathoracic pressure may be poorly tolerated in a patient with cardiorespiratory compromise.

1.Anesth 1974:41:242-255.2.J Clin Monit 1992:8: 251-252.

A.57

CONTINUOUS MONITORING OF THE VENTILATORY MECHANICS DURING ANAESTHESIA & INTENSIVE CARE

Carry Py*, Perdrix JP*, Baconnier P, Eberhard A**, Fargnoli JM**, Coppo F**, Banssillon V****

Department of Anaesthesia, Centre Hospitalier Lyon Sud* and PRETA, Fac. de Medecine, Grenoble, France**

Background and goal of study: Despite the high frequency of patients in the need of mechanical ventilation, few respiratory mechanical parameters can be monitored during anaesthesia and intensive care. We propose a system by which respiratory mechanics can be continuously monitored during these conditions.

Materials and methods: We continuously recorded tracheal pressure and flow (from the ventilator) in sedated patients subjected to controlled mechanical ventilation with constant flow insufflation and expiratory pause. A personal computer connected to the ventilator calculated 4 parameters: (1) **Rrs,Init**, e.g. the resistance of the respiratory system including the tracheal tube, (2) **Ers**, e.g. respiratory elastance, (3) **dPdiff/dT**, e.g. an estimate of the respiratory time constant inequality, and (4) **PEEPi**, e.g. the intrinsic positive end-expiratory pressure. These four parameters can be automatically calculated and stored over 24 h using a predetermined averaging period (expressed in min).

Results and discussion: After experimental adjustments of the four parameters, the system has functioned satisfactorily in patients during anaesthesia and intensive care conditions. These parameters can be obtained with a series of different ventilators, e.g. CFPO CESAR, PURITAN BENNETT 7200, SIEMENS-ELEMA 900C. Simultaneous recordings of tracheal pressure and flow signals by a Windograf Gould documented the accuracy of the measurements. The monitored PEEPi correlated well with PEEP measured during the end-expiratory paus.

Conclusions: We propose a system which reliably, non-invasively and automatically monitors respiratory mechanics during anaesthesia and intensive care.

A.58

CONTINUOUS MONITORING OF SpO2 DURING TOTAL INTRAVENOUS ANAESTHESIA WITH KETAMINE AND SPONTANEOUS VENTILATION

Luc-Marie Joly, Dan Benhamou

Département d'Anesthésie, Hôpital Antoine Béclère, Université Paris-Sud, 92141 Clamart, France

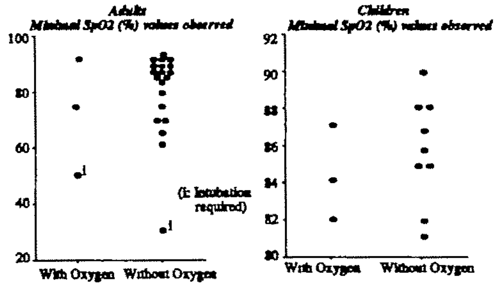
Background and goal of study: Total intravenous anaesthesia with ketamine (TIVAK) is widely used throughout the world especially in situations where oxygen is not easily available. When continuous monitoring of SpO2 was used in adult patients, few minor and transient desaturations were observed (1). However, several cases of respiratory distress have been reported and the safety of this technique has not been established in children.

Materials and methods: 76 adults and 64 children admitted at the Malte Order Hospital (Peshawar, Pakistan) from march to june 1992 and scheduled for peripheral surgery were randomised into two groups: Patients breathed either 40 % FiO2 (group 1) or room air (group 2) through a face mask from arrival in the operating room to complete recovery. Spontaneous ventilation was maintained throughout the study. Anaesthesia was started with 0.01 mg/kg of atropine, 0.1 mg/kg of diazepam and 2.5 mg/kg of ketamine. Then boluses of ketamine (1.25 mg/kg) were injected as required during surgery. SpO2 was continuously monitored using a pulse oxymeter and noted every five minutes. Respiratory events were recorded and a specific treatment was begun when SpO2 fell below 92 %. Statistics included two-way ANOVA for repeated measures and chi-square analysis as required.

Results and discussion: SpO2 decreased significantly 2 and 5 minutes after induction of TIVAK in adults breathing room air and 2 min after induction in children breathing room air. Respiratory events associated with desaturation occurred frequently in adults of group 2 (figure). One adult in each group required intubation immediately after induction (figure). In any patient was desaturation recorded later than 20 minutes after induction or during recovery.

Conclusion: Although SpO2 remained in the normal range during TIVAK and spontaneous ventilation in most patients, severe desaturations occurred, especially after induction in adults. Oxygen and equipment for intubation should be available.

Reference: 1- Pesonen MD: Pulse oxymetry during ketamine anaesthesia in war conditions. Can. J. Anaesth. 1991; 38:592-594.



A.59

HYPOXIC EVENTS AFTER GENERAL ANAESTHESIA IN THE RECOVERY ROOM

D Degasperi, M Vinelli, C Festa, MT Flandri

Department of Anaesthesia and Intensive Care, C Pizzardi Maggiore Hospital, Bologna, Italy

Background and goal of study: Several recent studies using pulse oximetry have identified preoperative risk factors associated with occurrence of hypoxaemic events after general anaesthesia, e.g. ASA physical status, surgical duration over 90 min, low preoperative SpO2 and history of smoking. We followed 85 patients after surgery and general anaesthesia to determine the incidence of hypoxaemia in the recovery room.

Materials and methods: Patients were monitored by pulse-oximetry with the probe placed on their index finger from arrival into the recovery room. SpO2 values were obtained 1, 5, 10, 15 and 30 min after arrival and hypoxaemia was arbitrarily defined as follows: 86-90% - mild, 81-85% - moderate, $\leq$ 80% - severe. If an SpO2 $<$ 90% was observed for more than 1 min patients received oxygen (FiO2 0.3 by Ventimask). If this proved insufficient FiO2 was increased by 0.1/min till SpO2 was above 90%.

Results and discussion: After 1 min we observed hypoxaemia in 23.5% of patients (age 55±14 y, ASA 1.4±0.7, SpO2 97±2, duration of surgery 166±101 min), after 30 min hypoxaemia was observed in 3.5%. After 5, 10, 15 and 30 min oxygen supplementation was given to 20%, 29%, 32% and 28% of patients respectively. The following risk factors for hypoxaemia in the recovery room were identified: duration and type of surgery (endocavitary), ASA physical status, preoperative SpO2 and presence of COPD. In general, over 30% of such patients were hypoxaemic during the first min, and 30 min later 40% needed oxygen supplementation. When comparing endocavitary surgery with superficial procedures we found the former to induce more hypoxaemia at 1 min (33% vs 12%, $p<0.05$), at 5 min (35% vs 13%, $p<0.05$) and the need for more oxygen supplementation at 10 min (41% vs 15%, $p<0.025$), at 15 min (46% vs 15%, $p<0.01$) and at 30 min (41% vs 13%, $p<0.01$).

Conclusion: We conclude that hypoxaemic events immediately after general anaesthesia are relatively frequent. Patients with risk factors have a higher incidence of hypoxaemia during the first postoperative min and have a greater need for supplementary oxygen which continues over the first 30 min.

Reference: M Denise Daley, et al: Hypoxaemia in adults in the post-anaesthesia care unit. Can J Anaesth 1991; 38: 740-6.

A.60

INFLUENCE OF ANAESTHESIA ON POSTOPERATIVE HYPOXAEMIA

Loucas Georgiou, Anastasia Vourlioti, Fani Kremastinou, Pantelis Stefanou, Adelais Tsiotou
Department of Anaesthesia
Hippokration General Hospital, Athens, Greece

Anaesthesia provokes hypoxaemia postoperatively, but the contribution of volatile versus i.v. anaesthetics to hypoxaemia is not established. The **aim of the study** was to compair the incidence and degree of hypoxaemia perioperatively.

50 non-obese patients (pts), ASA I-II, aged 25-65, who were scheduled for elective cholecystectomy with Kocher's incision, of less thal 1,5 hour duration, were randomly divided into two groups. Group A (24 pts) received total i.v. anaesthesia (T.I.A.) with propofol (PRO), while group B (26 pts) received volatile anaesthetic [Isoflurane (ISO)]. On the night before surgery (NBS), arterial oxygen saturation (SaO_2) was continuously monitored with a Novametrix pulse oximeter from 22:00 A.M. to 6:00 P.M. All pts received the same preoperative sedation, and postoperative analgesia. Group A received PRO for induction, and continuous PRO infusion for maintenance. Oxygen enriched air was used in ventilation (FiO_2-33%). Group B received pentothal for induction and a mixture of 67% N_2O in oxygen supplemented with ISO (1-1,5%) for maintenance. All other anaesthetic agents were the same for the two groups. SaO_2 was continuously monitored for 8 hours after extubation (early postoperative period - E.P.P.) and during the first (N_1), second (N_2) and third (N_3) night after operation. Results were analysed using Wilcoxon's signed rank test and Mann-Whitney U. test. Values are median values (range).

Results

MEAN OXYGEN SATURATION					
	NBS	EPP	N_1	N_2	N_3
Group A	95,47 (94-97)	95,3* (93-97)	94,71 (92-97)	94,2 (88-97)	95,4 (91-97)
Group B	95,37 (93-96)	94,64 (92-97)	94,37 (90-96)	94,37 (91-96)	93,6 (90-97)
MINIMUM OXYGEN SATURATION					
Group A	92 (82-94)	91*** (77-96)	92** (85-94)	91 (84-94)	92 (82-94)
Group B	92 (89-96)	90 (78-93)	88 (79-94)	90 (83-94)	90 (81-94)

* $p=0.03$ vs group B, ** $p=0.01$ vs group B, *** $p=0.008$ vs group B

During E.P.P. Mean SaO_2 was higher in Group A compared to Group B. During E.P.P. and N_1 SaO_2 was higher in Group A compared to Group B.

In **conclusion** total i.v. anaesthesia with propofol is superior to Isoflurane-N_2O anaesthesia, in terms of lesser hypoxaemia. The lower incidence of hypoxaemia might be explained by differences in pharmacokinetic and pharmacodynamic effects.

A.61

EARLY POSTPERFUSION ASSESSMENT OF GAS EXCHANGE AND POSTOPERATIVE EXTUBATION OUTCOME FOLLOWING CORONARY ARTERY SURGERY

P. Knapik, J.B. Richardson, I. McLellan
Department of Cardiothoracic
Anaesthesia, Groby Road Hospital, Leicester, U.K.

Background and goal of the study: Patients for elective coronary artery bypass grafting (CABG) with good preoperative lung function are foreseen as candidates for early extubation. The goal of this retrospective study was to find out whether the first postoperative arterial oxygen tension (PO_2) may indicate the duration of required respiratory support.

Materials and methods: 100 patients with normal lung function who underwent uncomplicated CABG, were studied postoperatively. Anaesthetic technique was similar in all cases with high dose opioid technique excluded. Under these circumstances the decision regarding extubation was undertaken on the basis of conventional criteria for non-cardiac cases. First postperfusion PO_2 was correlated with the duration of postoperative ventilation in hours for each patient and was also compared to this time at different ranges of PO_2.

Results and discussion: Correlation of PO_2 with time of ventilation in hours resulted in significant correlation coefficient of -0.574. Comparing the mean time of ventilation to the PO_2 resulted in significant differences between ranges with a narrow standard deviation for the group with high postoperative p02 level (see table below).

PO_2 (kPa)	Mean Vent (Hours)	Number of Patients	Standard Deviation
10-20	11.1	21	+-3.4
20-30	7.7	38	+-3.1
30-70	5.3	41	+-1.9

Conclusion: We conclude that first postperfusion PO_2 may be recognised as a simple and reasonably reliable predicting factor for the period of post operative ventilation especially if it exceeds 30 kPa in patients after uncomplicated coronary artery surgery.

References: 1. Higgins T.L. Pro-Early endotracheal extubation is preferable to late extubation in patients following coronary artery surgery. J. Cardiothorac. Anesth.1992,6,98-107.

A.62

CEREBRAL PERFUSION DURING OBSTRUCTIVE SLEEP APNEA (OSA).

Eva Bålfors and Karl Franklin

Departments of Anaesthesia and Lung Medicine, University of Umeå, Umeå, Sweden.

Background & goal of study: A high incidence of cerebral and cardiovascular complications is found in OSA. Intemittent negative intrathoracic pressure, arterial oxygen desaturation and variations in blood pressure, stroke volume, heart rate and intracranial pressure (ICP) have been described. Our goal was to study the association between systemic hemodynamics and cerebral circulation during sleep apnea (SA). For this purpose, we followed cerebral blood flow velocity (CBFV) and wave form pulsatility (Pi) during SA.

Patients & methods: 12 patients with severe OSA were studied during sleep. Simultaneous recordings of CBFV, mean arterial pressure (MAP), transcutaneous CO2 and O2 tensions (PtcCO2, PtcO2), O2 saturation (satO2) and respiratory movements were performed at baseline during normal sleep, and during and after SA-s.

Results & discussion: 219 CBFV-s were recorded during 34 SA-s (range 10-60 sec) in 6/12 patients who developed SA-s. MAP and CBFV varied typically during and after SA. MAP and CBFV increased gradually to reach a peak 11±6% and 15±6%, respectively, above baseline ($p<0.001$) at the end of SA, and decreased to 8±2% and 11±6%, respectively, below baseline ($p<0.001$) after the first breaths. They were back to baseline within 60 sec. If repetetive SA-s occurred, MAP and CBFV did not recover from their low values until breathing was normal. PtcO2 and satO2 decreased significantly while tcPCO2 did not change during SA. CBFV and MAP correlated (r=0.67), suggesting slow cerebral autoregulation. Pi decrased by 9±6% ($p<0.001$) after SA suggesting cerebral vasodilation. Pi increased (34±15%, $p<0.001$) during the low CBFV after SA suggesting increased ICP. The described changes were not seen while patients were awake or during normal sleep. We conclude that OSA is associated with major variations in CBFV, Pi and satO2. Reduced cerebral perfusion, arterial desaturation and increased ICP may all contribute to the cerebral symptoms described in OSA.

Reference: Podszus T, et al: Eur J Respir Dis 1986; (Suppl 146), 69:435.

A.63

RESPIRATORY EFFECTS OF LAPAROSCOPIC CHOLECYSTECTOMY (PRELIMINARY DATA)

MA Crea, L Sollazzi, V Perilli, E Marana, R Ranieri

Instituto di Anestesiologia e Rianimazione, Università Cattolica Sacro Cuore, Rome, Italy

Background and goal of study: Cholecystectomy by laparoscopic technique was first performed in 1987 (1) and can be applied to almost all patients with gallstones. Despite the rapid spread of this technique in the surgical community, there are few clincial anaesthesia studies. We report the respiratory and haemodynamic consequences of intraperitoneal carbon dioxide (CO2) insufflation for laparoscopy under general anaesthesia.

Materials and methods: 35 otherwise healthy patients suffering from symptomatic cholelithiasis were studied. After premedication, they were anaesthetized with isoflurane at 0.8 to 1.2% and mechanically ventilated. ECG, SBP, DPB, PAW, ETpCO2, ETiso, O2 saturation, arterial blood gases, intraabdominal pressure and insufflated CO2 volume (CO2vol) were recorded after induction of anaesthesia (T1), 5 min and 30 min after CO2 insufflation (T2 and T3) and 10 min after desufflation.

Results and discussion: There were no significant changes in haemodynamic parameters or paO2. paCO2 and ETpCO2 increased significantly at T2 and subsequently remained at these values (2,3). There were positive correlations between ETpCO2 and paCO2 at each measurement ($r=0.9$, $p<0.05$) and between paCO2 and CO2vol at T3 ($r=0.8$, $p<0.05$). Our data suggest minimal interference with gas exchange and mechanical ventilation. The amount of intraabdominally insufflated CO2 seems to induce an increase of paCO2 likely due to an absorption-diffusion phenomenon as indicated by the correlation between paCO2 and CO2vol.

Conclusion: Laparoscopic cholecystectomy is a safe technique in the healthy subject but should be safe also in patients with chronic obstructive lung disease and/or any other chest disease considering that laparotomy and major postoperative pain are avoided.

References: (1) Du Bois, et al: Ann Surg 1990;; 211:60-62, (2) Ali, et al: Am J Surg 1974; 128 (3): 376-382, (3) Rehder K, et al: Can Anaesth Soc J 1979; 26 (6): 451-462.

A.64

ABDOMINAL WALL RETRACTION MAY DECREASE ANAESTHESIOLOGICAL RISKS OF LAPAROSCOPIC CHOLECYSTECTOMY

Zsuzsanna Vereczkey, Barna Babik, János Fogas, Judit Méray, Béla Baltás.

Departments of Anaesthesiology and Surgery, Albert Szent-Györgyi Medical University, Szeged, Hungary.

Background and goal of study: The number of laparoscopic surgical and gynecological interventions has considerably increased in the last couple of years. The potential anesthesiological complications of these procedures have been extensively studied. Our aim was to reassess these problems in association with the use of a new surgical tool, the abdominal wall retractor (AWR).

Materials and methods: 20 patients were studied during laparoscopic cholecystectomy. 10 procedures were performed with conventional abdominal insufflation, and 10 with the use of AWR. Ataranaesthesia, intratracheal intubation and controlled mechanical ventillation were used. Parameters of the respiration were measured, the VCO2 vas registred by a mean stream capnograph (MSC), and percutanous pulsoxymetry (PPO) was also done. The cardiac output was detected by impedace cardiography, and the blood pressure was checked with a continuous non-invasive method.

Results and discussion : We found that an elevated pressure of CO2 in the peritoneal cavity caused considerable CO2 resorption with a concommittant increase in the VCO2 by 30 per cent. Decreased cardiac output was seen only in hypovolemic states, or at the time of PEEP ventillation. With the use of the AWR the intraabdominal pressure decreased from 12-15 mmHg to 5 mmHg ($p<0.05$). The volume of CO2 administred during the operation decreased considerably as well. The use of the AWR resulted in significant improvement in the parameters of mechanics of breathig. A decrease in the amount of absorbing CO2 was reflected in the significantly lower values of exhaled CO2 ($p<0.05$). The averege percutan O2 saturation was slightly higher in the AWR group (99% vs 97%, NS)

Conclusions: Based on our findings we hypothetise that the increased abdominal pressure results in increased airway pressures, dysteletasis of the basal pulmonal segments, and an increase in the intrapulmonary shunt circulation. The use of abdominal wall retractor may counteracts with this mechanisms. Abdominal CO2 absorption contributes significantly to the exhaled CO2 content. With the use of AWR this effect could be minimized.

A.65

DIAPHRAGMATIC FUNCTION AFTER BUPIVACAINE CERVICAL EXTRADURAL ANALGESIA FOR CHRONIC PAIN THERAPY

Elisabet Nyström, Erika Jansson, Britt-Inger Wenngren, Rajiv Sharma, Francois Clergue, Sebastian Reiz.

From the Departments of Anaesthesia and Otorhino-laryngology, University of Umeå, Umeå, Sweden and the Department of Anaesthesia, Tenon University Hospital, Paris, France

Background & goal of study: Extradural (ED) administration of steroids is a common therapy for cervical neurogenic pain and numbness due to osteoarthrosis. Most commonly, a local anaesthetic is used as carrier agent. The block consistently affects the nervous outflow to the diaphragm, which might potentially adversely affect respiratory function in patients with limited respiratory reserve. The aim of this study was to evaluate diaphragmatic function after cervical ED analgesia with bupivacaine used as carrier agent for depomedrone.

Patients & methods: 11 ambulatory patients with chronic pain due to osteoarthrosis were studied. They all had an ED catheter inserted to the C5 level via the C7/T1 interspace through which 3 ml at 5 mg/ml of bupivacaine mixed with 1 ml (40 mg) of depomedrone was injected after baseline measurements. These consisted of gastric (Pga) and oesophageal pressures (Poes), transdiaphragmatic pressure (Pdi), the relative contribution of rib cage and abdomen to quiet tidal breathing, and arterial blood gases. In addition, we assessed occulomotor function by EMG. All measurements were repeated 30 min after ED.

Results & discussion: The mean±SD spread of ED was from C3±0.6 to T6±1.2. Heart rate decreased from 75±12 to 69±9 bpm (p=0.013) as a sign of cardiac sympathetic blockade. Neither arterial blood gas tensions, nor Pdi were affected by ED. Respiratory rate and tidal volume remained unchanged (506±152 ml at control versus 441±180 ml after ED, p=0.068). The relative contribution of abdomen/rib cage to quiet tidal breathing remained constant at 73%/27%. Plots of $-\Delta Pga/\Delta Poes$ were not altered. Occulomotor function was signficantly impaired (p<0.0001). We conclude that cervical ED with a low dose bupivacaine (around 1.4 mg/segment) from C3 to T6 does not produce any evidence of diaphragmatic dysfunction or alteration of the contribution of rib cage and abdominal muscles to quiet breathing. It does, however, impair brain stem function as evidenced from decreased occulomotor function. This implies that adjacent respiratory nuclei could also be affected. The lack of alteration of respiratory function in our study could be explained by: 1. respiratory nuclei are more resistant to bupivacaine than occulomotor nuclei, 2. our techniques to explore respiratory function were less sensitive than the occulomotor test. Further studies with doses of bupivacaine used for surgical anaesthesia are needed to confirm the respiratory safety of cervical ED analgesia observed in the present study.

A.66

DIRECT, INDIRECT OR FLEXIBLE LARYNGOSCOPY AFTER THYROIDECTOMY ?

Louis Lacoste, Jérome Karayan, M. Suzanne Lehuedé, Pierre Ingrand, Jacques Fusciardi

Departments of Anesthesiology, Biostatistics and Surgery, Jean Bernard Hospital and University School of Medicine, 86021 Poitiers, France

Background and goal of study : After thyroidectomies it is recommended to perform a laryngoscopy to detect the possible laryngeal edema and nerve palsies (1-2). The goal of this prospective study was to compare three different methods of examination : direct (DL), indirect (IL) and flexible (FL) laryngoscopies.

Materials and methods : three hundred patients operated for thyroidectomy have been studied. After tracheal extubation, the patients were divided into two consecutive groups. In group I (n=200) we evaluated the efficiency of DL. In group II (n=100) we compared the efficiency, the duration, the easiness (+,±,-), and the side effects of the three methods of laryngeal examination. In each patient, the same anesthesiologist performed : DL 15 min after tracheal extubation, IL 15 min later and FL 15 min later (Olympus, LF-1). The efficacy of the laryngeal examinations was assessed by the ability to visualize the larynx on a scale 1-4 as described by Cormack and Lehane (3). The data were analysed using Chi-square test for the efficiency, Anova and Newman-Keuls tests for the duration, easiness and side effects, with p < 0.05 as significant.

Results and (discussion) : Grade 3 and 4 of Cormack and Lehane did not allow a sufficient laryngeal view to detect a glottic dysfunction. DL was ineffective in, respectively, 28% and 16% of the patients in group I and group II. With IL, failure occurred in 27% of the patients in group II. With FL, failure was limited to 1%. The duration of the three procedures was clinically similar (means-IL : 2 min, FL : 2.3 min and DL : 2.6 min), with DL slightly longer than IL. However, FL was easier to perform than DL and IL (+ = 96.5% versus 65% and 55%). The greatest cardiovascular variations were observed during DL. Systolic, diastolic, mean blood pressure (BP) and HR were both significantly higher with DL than with IL and FL. These side effects of FL consist of a slight increase in both HR (4 ± 7 beats per min) and systolic BP (3 ± 11 mmHg).

Conclusion : This study points out the flexible fiberoptic laryngoscopy as the best method for laryngeal examination after thyroidectomy. It is the most efficient, the easiest to perform and its side effects are not different from those of IL.

References :

1-Berlin DD, Surg Gynecol Obstet, 1935; 60:19-26
2-Martis C, et al, Am J Surg, 1971; 122:58-60
3-Cormack RS, et al,Anaesthesia, 1984; 39:1105-6

A.67

DAY 0 OR DAY 3 LARYNGOSCOPY AFTER THYROIDECTOMY ?

Louis Lacoste, Jérome Karayan, Daniele Thomas, Thierry Vallet, Jacques Fusciardi

Departments of Anesthesiology and Ear, Nose
and Throat Surgery, Jean Bernard Hospital,
86021 Poitiers, France.

Background and goal of study : After thyroidectomy, the anesthesiologist usually performs a laryngoscopy to detect laryngeal edema and nerve palsies. However the reliability of this immediate examination has been criticized (1). The goal of our prospective study was to compare the results collected by anesthesiologists on day 0 with the ones collected by the Ear, Nose and Throat (ENT) team on day 3.

Materials and methods : Six hundred and seventy four consecutive patients operated for thyroidectomy have been studied. After tracheal extubation, the patients underwent a laryngeal examination. On day 0, anesthesiologists used a direct laryngoscopy (DL) for the first 221 patients, and a flexible fiberoptic laryngoscopy (FL) for the following 463 patients. On day 3, all these patients were re-examined by the ENT team. After both examinations, vocal cord palsy and paresy (P) were recorded. For the analysis we left out the cases where the larynx could not be seen. Then we looked for the total number of P for the cumulated examinations (PO+P3). Next we analysed the evolution of P between day 0 and day 3 : how many of them disappeared (P3-), how many appeared (P3+), how many remained identical (P0=P3) and how many were recorded opposite (P0≠P3) ? Finally, we determined the value of day 0 examination achieved by the anesthesiologist.

Results and discussion : Inadequate laryngeal visualization accounts for the exclusion of 64 patients (DL:61, FL:2 and ENT:1). As a result, the records of 610 patients could be analyzed. The results are the following : P0+P3=92 (15%), P3-=21 (3.4%), P3+=25 (4.1%), P0=P3=40 (6.5%) and P0≠P3=6 (1%). Day 0 examination allows the detection of P3-, P0=P3 and P0≠P3. This concerned 67 cases representing 11%. Two high-risk patients were immediately detected. Day 3 examination allows the detection of P3+, P0=P3 and P0≠P3. This concerned 71 cases representing 11.6%. Our study confirms that P can be delayed after extubation (2). This occurred in 27.2% of P0+P3.

Conclusion : Laryngoscopy, on day 0, after thyroidectomy remains mandatory. Its rate of P detection is a good one, 73%. This permits a selection of high-risk patients. Since, 27% of P appeared secondarily, day 3 examination should be maintained though.

References :

1-Blackburn G, et al, Br J Surg, 1961; 48:371-3
2-Williams AF, Surgery, 1958; 435-9

A.68

LARYNGEAL FUNCTION AS ASSESSED BY TUSSOMETRY FOLLOWING TOPICAL ANAESTHESIA

R P Mahajan, G E Murty, P Singh, A R Aitkenhead
University Department of Anaesthesia, Queen's Medical Centre, Nottingham

Background and goal of study: Tussometry is a new non-invasive method of assessing laryngeal function which allows the assessment of laryngeal function by analysis of the airflow waveform produced by a voluntary cough. A normal wave is displayed as cough flow rate (l min^{-1}) against time (ms) and shows a rapid rise to a peak - the cough peak flow rate (CPFR). The time taken to reach CPFR, the peak velocity time (PVT), correlates with vocal cord function [1] and is potentially a useful indicator of laryngeal function in patients undergoing anaesthesia [2]. There is a paucity of data indicating motor function of the vocal cords following topical anaesthesia. We have employed tussometry to determine whether or not topical anaesthesia has any effect on motor function of the vocal cords.

Materials and methods: After baseline measurements of CPFR and PVT, five healthy volunteers, four males and one female (mean age 37.2 yr (range 31-52), mean weight 77.4 kg (range 60-88) and mean height 1.77 m (range 1.7-1.85)) received topical anaesthesia of the nose by a nasal swab soaked in 4% cocaine. Indirect laryngoscopy was performed and the larynx was anaesthetised topically using ten metered dose sprays of lignocaine (100 mg). A fibreoptic laryngoscope was then passed nasally to visualise the larynx. The vocal cords were touched with the scope and if no coughing occurred, the scope was removed and repeat measurements of CPFR and PVT were made.

Results and discussion: All volunteers had excellent anaesthesia of the larynx. No coughing was elicited on fibreoptic laryngoscopy even when the vocal cords were deliberately touched. However, on voluntary coughing, topical anaesthesia had no effect on PVT, indicating normal vocal cord function (Table). All subjects had great difficulty in swallowing.

Table. CPFR and PVT following topical anaesthesia

	CPFR (l min^{-1})		PVT (ms)	
	Before	*After*	*Before*	*After*
Mean	701.6	649.0	28.6	29.4
SD	190.2	100.1	5.9	4.4

Conclusion: Our results indicate that topical anaesthesia of the larynx does not impair voluntary motor function of the vocal cords.

References

1. Murty GE, Lancaster P, Kelly PJ. *Clin Otolaryngol* 1991; 16: 249-51.
2. Lamb JM, Murty GE, Slater RM, Aitkenhead AR. 1993 *Brit J Anaes* (in press).

A.69

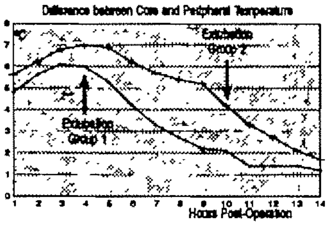
CORE-PERIPHERAL TEMPERATURE DIFFERENCE IN EARLY VS LATER EXTUBATION AFTER CORONARY ARTERY SURGERY.

P. Knapik, J.B. Richardson, I. McLellan
Department of Cardiothoracic
Anaesthesia, Groby Road Hospital, Leicester, U.K.

BACKGROUND AND GOAL OF THE STUDY: Increasing popularity of coronary artery surgery has led to a reappraisal of the need for prolonged postoperative respiratory support after uncomplicated hypothermic cardiopulmonary bypass. Early extubation after open heart surgery in selected patients decreased the core-peripheral temperature gradient and therefore shortened the rewarming period. Testing this observation is the aim of this study.

MATERIAL AND METHODS: Fifty patients who underwent uncomplicated coronary artery bypass surgery and were extubated 4 hours(group I, n=25) and 10 hours (group II, n=25) after termination of cardiopulmonary bypass (CPB) were studied postoperatively. All the patients were cooled to 28°C. Statistical analysis of postoperative core and peripheral temperatures as well as important entry criteria was performed.

RESULTS AND DISCUSSION: Patients extubated 10 hours after weaning from CPB had significantly lower initial core temperatures. The differences between the core and peripheral temperatures were not significant up to the fifth postoperative hour and then became significant with group I rewarming quicker than group II as seen below.



CONCLUSION: Earlier extubated patients with higher initial core temperature are warming up quicker peripherally after uncomplicated coronary artery surgery.

REFERENCES: Sladen R.N. Temperature changes and ventilation after hypothermic cardiopulmonary bypass. Anesth. Analg. 1985,64,816-820.

A.70

EFFECTIVENESS OF CORE WARMING ON NET TRANSFER OF BODY HEAT ACROSS THE SKIN

P Kulkarni, F Carli

Department of Anaesthesia, Northwick Park Hospital and Clinical Research Centre, Harrow, England.

Background and purpose of the study: Body heat loss can occur during anaesthesia and surgery. Residual hypothermia at the end of surgery can represent a major metabolic load in the high risk population such as elderly with poor cardiovascular reserves.

The effectiveness of measures aiming to attenuate the intraoperative fall in body temperature is assessed by the capacity to maintain core temperature within normal limits and to attenuate the loss of body heat across the skin.

Patients and methods: Thirty elderly patients (age range 60-88 years), otherwise healthy, scheduled for elective total hip replacement, were randomly allocated to 3 groups: group A (control, n=10) with no active warming, group B (hot water humidifier, set at 40°C at mouth level, n=10) and group C (oesophageal warming device, set at 40°C). Premedication was with papaveretum and general anaesthesia consisted of thiopentone, vecuronium, enflurane, N_2O/O_2. Operating theatre ambient temperature was between 18.7 and 21.8°C. Body temperature was recorded in the aural canal (core) and at 15 skin surface sites (mean skin calculated from unweighed formula) before induction of anaesthesia and at the end of surgery and anaesthesia.

Results and discussion: Core temperature fell significantly in group A and C by 1.9 and 1.3°C respectively ($p<0.01$). On the contrary, there was a fall of 0.3°C in the group B (humidifier) (NS). In the latter group mean skin temperature increased from a mean of 34.05°C (SD, 0.31) to 34.21°C (SD, 0.3), whilst in group A, it fell from 33.6° C (SD, 0.8) to 32.5°C (SD, 0.7). In group C (oesophageal warming device) there was a mean fall of 0.2°C in mean skin temperature.

The results of this work show that body heat conservation in elderly patients having hip arthroplasty in a cold environment, is obtained by using hot water humidifier in the anaesthetic circuit.

A.71

EFFECT OF PREMEDICATION WITH NIFEDIPINE ON INTRAOPERATIVE HYPOTHERMIA

Vassilieff N*, Rosencher N,* Sessler D.I.***, ConseillerCh* Lienhart A.**

Departments anaesthesia and intensive care COCHIN *and St Antoine** hospitals Paris FRANCE
Department of anesthesia ,University of California San Fransisco***U.S.A.

Introduction: Initial hypothermia is mainly due to redistribution of heat between peripheral and core compartments[1]. In a preliminary , retrospective study Nifedipine, a calcium blocking agent, given days before anaesthesia, has been shown to reduce the initial hypothermia[2] We present a new prospectived and randomized study done in order to confirm these results without statistical bias.

Methods: After obtaining informed consent, 30 patients (ASA 1 or 2) scheduled for total hip arthroplasty were randomly divided into 3 groups. 10 patients received 20 mg Nifedipine long acting orally 12 hours before surgery then 10mg 1h30mn before induction (NPm group). 10 patients received 10mg Nifedipine sublingual immedlatly before induction of anaesthesia (Nind group). 10 patients received no Nifedipine(C group). Core temperature (T core) was continuously measured using tympanic and esophageal probes. Skin T were measured at 5 sites every 10 min for the same periods and mean skin T (MST) calculated. Heart rate and blood pressure were monitored every five minutes. Results (means ± SEM) were compared using ANOVA, modified t-test or Fisher's exact test as required.

Results: The three groups did not differ in age, weight, operating room T ,heart rate ,blood pression and duration of anaesthesia. During the 30 min following induction of anaesthesia, Tcore decreased in the three groups but hypothermia developed less rapidly in the NPm group than in the other group (fig.1.)The final part of the curves are almost parallel.At the end of surgery,Tcore is lower in Nind group (33.43±0.31°C)and in Cgroup(33.58±0.35°C),than in NPm one (34.52±0.35°C). MST remained stable during the surgery in the C group while it increased until the 40th min in the two Nifedipine groups.

Discussion: These results indicate that Nifedipine in normal subjects, given many hours before anaesthesia, reduces core hypothermia .It is probably due to heat redistribution hours before induction. An effect on thermoregulation mechanism is unlikely since the decrease in T core is similar in C group and Nind group.

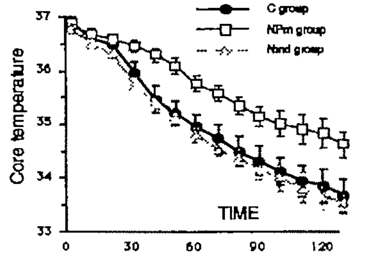


fig 1

References .
1 Vassilieff N Ann SF Anesth-reanim 11 484,1992
2 Seesler D Anesthesiology 74 226 1991

A.72

PREOPERATIVE SKIN-SURFACE WARMING REDUCES INTRAOPERATIVE HYPOTHERMIA.

Camus Y, Delva E, Lienhart A.

Department of Anaesthesia and Intensive Care
Saint Antoine Hospital, Paris, France

Introduction: Induction of anaesthesia is followed by a rapid decrease in core temperature which largely results from redistribution of heat from the core to the cooler periphery.[1] Decreasing the central-peripheral temperature gradient before induction by skin-surface warming largely prevents initial hypothermia in volunteers.[2] The aim of this study was to evaluate the efficacy of preanaesthesia skin-surface warming in reducing intraoperative hypothermia under surgical conditions.

Methods: After informed consent and institutional approval,16 ASA I-II patients, scheduled for laparoscopic cholecystectomy, were randomly divided into 2 groups. 8 patients were preoperatively covered up to the shoulders with an air blanket attached to a forced-air warmer Bair Hugger set at high (≈ 43° C) during 60 min (prew.) while 8 other patients were not (cont.). No special precautions were taken intraoperatively to avoid hypothermia. Core temperature (T) was continuously recorded using a tympanic probe, preoperatively during 1 h (preop) then intraoperatively. Skin T were measured at four sites every 15 min for the same periods and mean skin T (MST) calculated.[3] Results (means ± SEM) were compared using ANOVA, modified t-test or Fisher's exact test as required.

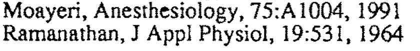
Results: The two groups did not differ in age, weight, operating room T and duration of anaesthesia (128 ± 7 min). Main results are shown in the table and the figure.

Table	MST (° C) end proop	Core T (° C) end preop	Core T (° C) 60 min Intraop
Cont.	34.7 ± 0.3	36.9 ± 0.2	36.0 ± 0.1
Prew.	37.0 ± 0.2 ★	37.2 ± 0.1	36.6 ± 0.1 ★

★ = $p < 0.05$ vs control group.

At the end of surgery core T was 36.1 ± 0.1° C in the prew. group *vs* 35.7 ± 0.1° C in the cont. goup ($p < 0.05$).

Discussion: Preoperative skin-surface warming significantly minimized the initial decrease in core T. This result is in agreement with the importance of internal heat redistribution during the early phase of anaesthesia. It was also sufficient to significantly reduced core hypothermia until the end of laparoscopic surgery lasting ≈ 2 hours.



References .
1 Sessler, Anesthesiology, 74:226, 1991
2 Moayeri, Anesthesiology, 75:A1004, 1991
3 Ramanathan, J Appl Physiol, 19:531, 1964

A.73

AN INVESTIGATION INTO THE EFFECT OF PASSIVE AND ACTIVE CUTANEOUS WARMING DEVICES ON INTRAOPERATIVE BODY TEMPERATURE IN ELDERLY PATIENTS

J Bennet, V Ramachandra, F Carli

Department of Anaesthesia, Northwick Park Hospital and Clinical Research Centre, Harrow, England

Background and purpose of the study: Hypothermia is an inevitable consequence of anaesthesia and surgery, and age represents one of the most important factors contributing to a fall in intraoperative body temperature. Providing thermoneutrality during anaesthesia has metabolic and physiological advantages for the elderly patient. Since most of heat is lost through the skin,prevention of cutaneous heat loss might attenuate the fall in central temperature during surgery. The purpose of this study was to assess the effectiveness of skin passive and active warming on maintenance of intraoperative nomothermia.

Patients and methods: Twenty one elderly patients (age range 62-85 years) scheduled for elective hip replacement were randomly allocated to 3 groups of 7 patients each. Group A (control) received no warming, whilst patients in group B (passive warming) were covered with metallised plastic sheet (Thermodrape). In group C (active warming) forced warm air system (Bair-Hagger) was implemented. Ambient temperature in the operating theatre was between 18.4 - 21.1°C. Patients were premedicated with papaveretum, and general anaesthesia was with thiopentone, vecuronium, enflurane, $N_20/0_2$. Core temperature (aural canal thermocouple probe) was measured before induction of anaesthesia and at the end of surgery and anaesthesia. Duration of surgery ranged between 110-175 min.

Results and discussion: Core temperature decreased significantly in the control group (A) from a mean value of 36.6°C (SD, 0.4) to 35.2°C (SD, 0.4) and in passive warming group (B) from 36.8°C (SD, 0.4) to 35.6°C (SD, 0.5) ($p<0.001$). On the contrary, in the active warming group (C) there was a small fall in core temperature throughout surgery, from 36.6°C (SD, 0.3) to 36.2°C (SD, 0.4). These preliminary results show that application of active warming on the exposed parts of the body can significantly attenuate the fall in core temperature and prevent cutaneous heat loss in a selected population of elderly. It remains to be seen whether an extended application of this system to major abdominal/thoracic syrgery maintains perioperative normothermia.

A.74

FENTANYL, AS PETHIDINE, INHIBITS POST ANAESTHESIA SHIVERING

Pascal Alfonsi, Jean-Marc Hongnat, Claude Lebrault, Marcel Chauvin

Department of Anaesthesia, Hopital Ambroise Paré, Boulogne, France

Background and goal of study: Several studies show that pethidine inhibits the Post-Anaesthesia Shivering (P.A.S.) (1). Inversely, other opiates fail to do it (1). The pethidine's efficiency may be the result of its local anaesthetic properties (2). An other reason is that, in the previous studies, the authors did not compare the drugs with an equipotent dosage. The goal of this double-blind controlled study was to compare the effects of pethidine (P), fentanyl (F) and lidocaine (L), versus placebo (C), on P.A.S. .

Materials and methods: In recovery room, after a general anaesthesia, 40 patients with a physical status ASA 1 or 2 were included. They all presented shiverings associated with a tympanic temperature below 36°C. None presented an allergy for local anaesthetic. The patients received: P (n=13; 0.85mg/kg) F (n=13; 1,7 mcg/kg) L (n=7; 1 mg/kg) C (n=7; Ringer-Lactate's solution). All the solutions were injected in a 10 ml volume. At the 15th min. (T15), the patients who were still shivering were excluded. Shiverings were evaluated all the time by the same investigator.

Results and discussion: The patient's and anaesthetic's charateristics are summarized in Table 1. At T15, 100% in C still presented P.A.S., 86% in L, 23% in F($p<0.01$ vs C) and 8% in P($p<0.001$ vs C). When the patients had stopped shivering, all of them were hypothermic (35.1±0.6°C in P and 35.9±0.5°C in F). From T15 to T45, 60% of patients receiving F and 8% receiving P had again presented P.A.S.

Conclusion: Our results show that fentanyl, as pethidine inhibits P.A.S. In the previous studies (1), fentanyl have been probably used with an insufficient dosage. This result confirms that the effects of opiates on shiverings are mediated by opiates receptors (3).

References: 1. Pauca AL, et al; *Acta Anaesth Scand* 1984; 28: 138-143. 2. Glosten B,et al; *Anesth.Analg.* 1990; 70 (Suppl): S127. 3. Cooper JO, et al; *Anesthesiology* 1990; 73 (Suppl): A230

	Age	Height (cm)	Weight (kg)	Anesth. (min)	Temp. (°C)
P	49±13	169±12	63,3±12	130±54	34.7±0.9
F	43±13	175±5	68±9	128±42	35.2±0.6
L	36±11	174±11	64±15	143±69	34.9±0.5
C	45±11	175±5	71±10	152±100	35.3±0.6

Table I.: no differences (mean±sd)

A.75

MODIFICATION OF THE RENIN-ALDOSTERONE AXIS DURING ORTHOTOPIC LIVER TRANSPLANTATION

De los Ríos J., Iribarren MªJ, Monedero P, García-Pedrajas F, Arroyo JL
Anesthesiology Department. Clínica Universitaria. School of Medicine. University of Navarra. Pamplona. Spain.

Introduction: Several studies have demonstrated that the activation of the renin-angiotensin-aldosterone (RAA) system is an important cause of renal sodium retention in cirrhosis. We have evaluated the changes in plasma renin activity (PRA), plasma aldosterone (PA) concentrations and urinary excretion of sodium (mEq/24 h) (UENa) in patients undergoing orthotopic liver transplantation (OLT) with preoperative high levels of renin and aldosterone and low renal sodium excretion.

Methods: We studied 16 patients with main diagnosis of cirrhosis, scheduled for OLT who fulfilled all criteria required by the protocol of our institution. Renal function profile was included within preoperative study. No patient was on antihypertensive therapy. Eleven patients were treated with spironolactone and 2 patients were with low sodium diet. No patient was azotemic and none had intraoperative events in terms of hemodynamic stability and renal function. A standard anesthesia technique was used. We measured PRA and PA before surgery and in the morning of the next four postoperative days. All patients were studied following our postoperatory protocol for OLT.

Results: In the four postoperative days the PRA and PA values were significantly lower than basal value. There were no differences in cardiac output and hemodinamic parameters between preoperative and the first postoperative day. On the other hand, UENa was significantly raised in the postoperative days compared with basal values.

	BASAL	DAY1	DAY2	DAY3	DAY4
PRA ng/ml/min	10.7±8.2	7.4±11	1.3±1.2*	1.2±0 8*	0 6±0.7*
ALD ng/ml	628±525 2	202±210.5*	65.5±40 1*	64±44 4*	54.8±32.8*
UENa meq/ 24h	74.5±48.3	259±146*	375±168*	418 2±189*	341 1±120*
CO L / mn	9±4 05	9 5±2.7	8 9±2.2		
SVR dyn s cm-5	794±422	631±228	810±210		
MAP mmHg	83±15	80±12	85±17		
PCWP mmHg	11±2 9	13±2.4	13±3.1		

* p<0.05

Discussion: It is concluded that in patients with stimulated RAA system by cirrhosis, a fall in PRA and PA after OLT ocurred postoperatively, which could be interpreted as physiological inhibition of this system due to the fluid volume received during the intraoperative and the four postoperative days. We explain the important natriuresis observed during the postoperative period as a consecuence of the inhibition of the RAA system and other mechanisms which produce renal sodium retention in cirrhosis.

Reference: Aliaga L, et al. Renal hemodynamics and the Renin-Angiotensin System in Cirrhosis: Rev Esp Fisiol 1989; 45 (Suppl.): 371-6.

A.76

MEASUREMENT OF SIGMOID INTRAMURAL PH DURING ORTHOTOPIC LIVER TRANSPLANTATION.

Yves Auroy, Marie-Christine Gillon, Henri Bismuth*, Claude Ecoffey.

Département d'Anesthésie - Réanimation et *Service de Chirurgie hépato-biliaire, Hôpital P. Brousse, Université Paris-Sud, 94804 - Villejuif, FRANCE

Background and goal of study: The presence of sigmoid intramural acidosis, as measured by balloon tonometry, has been shown to be predictive of a higher incidence of complications in postoperative patient (1). A relationship was found between low sigmoid intramural pH (pHi) values were causally related to changes in gut perfusion which can induced ischemic colitis (2). During orthotopic liver transplantation (OLT) a decrease in splanchnic perfusion can occurred during the anhepatic phase (3) and we assessed the evolution of the pHi during the different stages of OLT.

Material and methods: Ten patients aged 49 ± 11 yrs (mean ± SD) who underwent OLT were studied. After induction of anaesthesia, a radial artery catheter, a Swan Ganz catheter and a silicone balloon tonometry (TRIP*TS 1001) were placed. The balloon was introduced until the junction between the rectum and the sigmoid colon. The following measurements were performed: mean arterial pressure (MAP, mmHg), cardiac index (CI, $min^{-1}.m^{-2}$), arterial pH (pHa, unit), mixed venous pH (pHv, unit), pHi (unit), and arterial lactate (Lact, $mmol.l^{-1}$). The measurements were assessed during the dissection phase (T1 and T2), during the anhepatic phase (T3) and during the reperfusion phase (T4, T5 T6, respectively one, two, three hours after unclamping the hepatic vessels). The pHi value was calculated with Henderson-Hasselbalch equation with the use of arterial bicarbonates. All the results are expressed as mean ± SD and a statistical analysis ($p < 0.05$ significant) was performed with ANOVA following by Fischer test.

Results and discussion : A veno-venous bypass was used in 8 patients. One patient received 200 ml of molar sodium bicarbonate after the reperfusion phase and the values of pHi were excluded of the analysis. The results are summarized in the table:

mean (SD)	T1	T2	T3	T4	T5	T6
PAM	101	103	104	92	92	99
	(15)	(15)	(21)	(17)	(18)	(20)
CI	3.9	4.0	2.4*	4.1	3.7	3.5
	(1.1)	(0.7)	(0.7)	(0.7)	(0.7)	(0.5)
pHa	7.44	7.44	7.45	7.40	7.42	7.44
	(0.04)	(0.04)	(0.02)	(0.02)	(0.04)	(0.04)
pHv	7.43	7.43	7.42	7.37*	7.40	7.41
	(0.04)	(0.03)	(0.03)	(0.04)	(0.06)	(0.03)
pHi	7.34	7.32	7.25*	7.33	7.34	7.33
	(0.08)	(0.09)	(0.08)	(0.08)	(0.10)	(0.10)
Lact	1.9	2.3	3.7*	3.9*	3.1	2.5
	(0.7)	(1.0)	(0.9)	(1.0)	(0.7)	(0.1)

* $p < 0.05$ vs other measurements

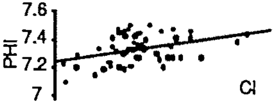


Figure: Relationship between pHI (unit) and CI ($l.min^{-1}.m^{-2}$)
$y = 0.03 x + 7.2$
($n = 54$, $r = 0.4$, $p< 0.01$)

Conclusion: The transient changes of pHi during OLT indicated probably a decrease in gut perfusion, due in part to the decrease in CI, without ischemic colitis complication. Further measurements should be taken after the reperfusion phase in order to detect an possible ischemic colitis.

References: 1) Fiddian - Green et al. Arch Surg 1986; 121: 854-860. 2) Schiedler et al. Arch Surg 1987; 122: 881-886. 3) Shaw et al. Ann Surg 1984; 200: 524-533.

A.77

CHANGES IN BLOOD LACTATE, TOTAL BODY OXYGEN DELIVERY AND CONSUMPTION DURING LIVER TRANSPLANTATION

Carrera J, Monedero P, Iribarren MJ, de los Ríos J, Panadero A

Department of Anaesthesiology, Clínica Universitaria, School of Medicine, University of Navarra, Pamplona, Spain

Introduction: The liver, perfused by approximately 25 per cent of the cardiac output, has a large oxygen consumption and plays a central role in lactate metabolism for acid-base homeostasis. The O2-uptake and lactate concentrations during 36 orthotopic liver tranplantations (OLT) were studied to know their changes during this procedure.

Methods: Cardiac output and central venous oxygen saturation were measured by an oximetric-type pulmonary artery catheter, after anaesthetic induction (basal sample, B) and during each of the three operative periods (I: dissecting period-preanhepatic; II: anhepatic phase; III: after reperfusion of the new liver): 60 and 120 minutes after incision (IA, IB); 30 minutes after removal of the liver (IIA); and 10, 60 and 120 minutes after graft reperfusion (IIIA, IIIB, IIIC). Samples of arterial blood were taken simultaneously for lactate and hemoglobin blood concentration and arterial oxygen saturation. The index of total body oxygen delivery (IDO2) and consumption (IVO2) was calculated.

Results and Conclusions: Results are shown in table I.

The IVO2 decreased after removal of the liver (IIA), and increased after reperfusion (IIIA, IIIB, IIIC). The level of IVO2 was higher after reperfusion (IIIA) than in the dissecting period (IA, IB).

Lactate levels increased during the surgical procedure, mainly during the anhepatic phase (IIA), and began to decrease 2 hours after reperfusion (IIIC). Six patients with bad postoperative liver function (3 of them required retransplantation) showed higher lactate levels than patients with good evolution (Lactate IIIB: good evolution 5.6 (1.8) versus bad evolution: 8.3 (2.1); $p<0.05$ Mann-Whitney U). (Lactate IIIC: good evolution 5.2 (2.0) versus bad evolution: 7.6 (0.7); $p<0.05$ Mann-Whitney U). We conclude that lactate concentrations may have a pronostic value in OLT.

Table I : IDO2, IVO2 and lactate during OLT: mean (SD)
(ml/min/m2) (mM/L)

	B	IA	IB	IIA	IIIA	IIIB	IIIC
IDO2	640 (213)	736 (228)	705 (224)	413 (142)	943 (313)	788 (266)	733 (168)
IVO2	109 (41)	103 (30)	93 (28)	81 (62)	131 (51)	121 (35)	117 (32)
Lactate	1.8 (1,3)	2.1 (1,1)	2.6 (1,0)	4.5 (1.6)	5.8 (1.7)	5.9 (1.9)	5.4 (2.0)

Reference: Anaesthesist (1988) 37: 211-217.

A.78

OXYGEN CONSUMPTION IS DEPENDENT UPON OXYGEN DELIVERY IN CIRRHOTICS UNDERGOING LIVER TRANSPLANTATION

Pasquale Piccinni, Antonio Tripepi, Lorenzo Rossaro*, Francesco De Zen, Antonino Pierri.

Servizio di Anestesia e Rianimazione,
*Gastroenterologia, Universitá di Padova, Italy

Background and goal of study: Hepatic failure secondary to chronic liver disease is associated with an hyperdynamic state characterized by an increased cardiac index, low systemic vascular resistance, and abnormal tissue oxygenation[1]. The relationship between oxygen uptake (VO_2I) and systemic oxygen delivery (DO_2I) in cirrhotic patients is not known. The aim of the present study was to evaluate such a relation (VO_2I/DO_2I) during each phase of orthotopic liver transplantation (OLTx).

Materials and methods: We performed a complete hemodynamic study in ten adult cirrhotic patients who underwent OLTx, with constant temperature, stable hemoglobin levels during homogeneous anaesthesiological and technical procedures, which included also venous-venous bypass. We used a rapid response thermodilution pulmonary artery catheter (Swan-Ganz, 93A-431H-7.5F, Baxter) and a gas analyzer (Oxymetrix 3 Computer, Abbott) which provided continuous measurements of venous oxygen saturation ($S\bar{v}O_2$) and thereby enabled us to calculate VO_2I and DO_2I. Hemodynamic profiles were determined at different times during OLTx: (1) basal, (2) 30 min before and (3) during the anhepatic phase, (4) 5 min and (5) 30 min after reperfusion of the graft.

Results and discussion: A direct linear correlation was observed during each phase of OLTx between VO_2I and DO_2I ($R=0.7393$, $p<0.01$), demonstrating a strong dependance of oxygen consumption upon oxygen delivery.

Conclusion: We hereby report, for the first time, the dependance of oxygen consumption upon oxygen delivery in cirrhotic patients undergoing liver transplantation. This abnormal finding must be further evaluated and confirmed on a larger series. Meanwhile, our observations suggest the important role of maintaining effective tissue oxygenation by adequate DO_2I levels during liver transplantation.

Reference: 1. Moreau R. et al: Abnormal tissue oxygenation in patients with cirrhosis and liver failure. J Hepatol 1988; 7:98-105.

A.79

EFFECTS OF DESMOPRESSIN (DDAVP) SUPPLEMENTATION IN BRAIN DEAD ORGAN DONORS (BDOD) ON EARLY RECIPIENT RENAL FUNCTION

Richard Guesde, Salda Ourahma, Bruno Riou, Pierre Viars

Department of Anaesthesia and Intensive Care,
Groupe Hospitalier Pitié-Salpêtrière, Paris, France

Background and Goal of the Study : Treatment of central diabetes insipidus (DI) is required during BDOD care to avoid major metabolic disturbances and premature cardiac standstill Replacement of massive water and potassium losses is difficult to achieve and vasopressin-related post-transplantation renal dysfunction has been suggested. The use of DDAVP instead of vasopressin in BDOD has not yet been assessed.

Patients and Methods : Retrospective data concerning 42 consecutive BDOD (15 of which received DDAVP to decrease hyperdiuresis) were studied. and those from 78 of the 80 corresponding recipients (26 of which benefited from DDAVP-supplemented kidneys). obtained by queries. were analyzed up to the fifth posttransplantation day. Data are expressed as mean ± sd

Results :Both groups of BDOD were similar with respect to sex ratio. age. and occurrence of hypotension. 14 of the 15 DDAVP donors required dopamine (7.9 ± 5.0 μg/kg/min) versus 19 of the 27 others (7.0 ± 4.4 μg/kg/min) in order to maintain adequate haemodynamics. this difference did not reach statistical significance. Maximum urine output was higher in the DDAVP group (1530 ± 814 vs 1001 ± 730 ml. $p<0.01$). while last urine output before harvesting was similar in both groups (900 ± 1221 vs 628 ± 642 ml.). All BDOD but two in the non-DDAVP group became multiorgan donors.

Both groups of recipients were similar with respect to factors influencing early renal outcome : age. occurrence of diabetes and hypertension. cold and warm ischaemia times. number of HL-A.-B.-DR mismatches. preoperative serum creatinine levels and need for early reoperation. Immediate urine output was higher in the DDAVP-recipient group during the 4th and 5th posttransplantation hours. Daily serum creatinine decay rate was not different between groups. Posttransplantation needs for dopamine and furosemide. occurrence of acute tubular necrosis requiring haemodialysis (7/28 vs 14/50) were not different

Conclusions · Kidneys harvested from DDAVP treated BDOD showed a good early renal recovery. similar to those from unsupplemented donors DDAVP given to decrease major polyuria in BDOD did not seem to be detrimental to early renal transplant function. The lack of vasopressin-associated vasoconstriction may explain this result. A prospective randomized study is now undertaken to demonstrate that the beneficial effect of DDAVP on BDOD care is also beneficial to recipient renal function.

A.80

FIBEROPTIC BRONCHOSCOPY IN BRAIN DEAD ORGAN DONORS.

Bruno Riou, Richard Guesde, Yves Jacquens, René Duranteau, Pierre Viars.

Department of Anesthesiology, CHU Pitié-Salpêtrière,
University Paris VI, Paris, France.

Background and goal of the study: The quality of the donor lungs is one of the most significant predictors of the clinical outcome of pulmonary and cardiopulmonary transplantations. Criteria for selecting lung donors include normal chest X-ray and adequate gas exchange, but a normal fiberoptic bronchoscopy (FO) is not always required. We conducted a prospective study of FO in brain dead donors scheduled for a multiple organ procurement.
Patients and methods: Criteria for inclusion were : 1/brain death ; 2/multiple organ procurement was scheduled ; 3/FO (Olympus BF10) could be performed by a highly trained bronchoscopist before going to the operating room. Chest X-ray was performed in a supine position and analyzed by a blind observer (normal/abnormal), arterial blood gas analysis was performed under an FiO_2 of 100 %. The following FO diagnosis could be made: 1/normal; 2/inhalation of blood; 3/inhalation of gastric contents; 4/pulmonary contusion; 5/purulent bronchial secretions. Cardiac evaluation was performed using a Swan-Ganz catheter or transesophageal echocardiography.
Results: 72 brain dead donors were included, mean age 38±13 yrs. Chest X-ray was normal in 37 (51%) donors, and the PaO_2 was greater than 400mmHg with an FiO_2 of 100 % in 34 (47%) donors. FO was normal in only 24 (33 %) donors. In the remaining 48 donors, inhalation of blood (n=17) or gastric contents (n=16), pulmonary contusion (n=5), or purulent bronchial secretions secretions (n=9) were noted. In the 26 donors with normal chest X-ray and a PaO_2 greater than 400 mmHg with an FiO_2 of 100%, FO was abnormal in 10 (38%) donors. In 33 donors with a Swan-Ganz catheter, the arteriovenous difference in oxygen content (2.4±0.8mlO2/100ml), and pulmonary shunt (0.30±0.11, range 0.13-0.49) were measured. In the 15 donors with a PaO_2 greater than 400mmHg, pulmonary shunt was 0.23±0.07, range 0.13-0.35.
Conclusion: Chest X-ray and arterial blood gas analysis are not sufficient, and FO should be routinely performed to select lung donors. In donors with a normal FO, measurement of pulmonary shunt, and not only PaO_2, should be performed to assess pulmonary gas exchange.

A.81

TOTAL INTRAVENOUS ANAESTHESIA (TIVA) WITH PROPOFOL AND ALFENTANIL FOR RENAL TRANSPLANTATION

M. Kirvelä, A. Yli-Hankala, L. Lindgren

Department of Anaesthesia, IV Clinic of Surgery,
Helsinki University Hospital, Helsinki, Finland

The pharmacokinetics of propofol (1) and alfentanil (2) are similar in uraemic and healthy patients. We compared TIVA with propofol and alfentanil to balanced anaesthesia (BA) for renal transplantation.

Patients and methods: 30 uraemic patients undergoing renal transplantation were anaesthetized with either TIVA (15 pts, mean (SD) age 37(11) yr, weight 67(9) kg) or BA (15pts, 42(13) yr, 72(11) kg). TIVA was induced with propofol 2-2.5 mgkg^{-1} and alfentanil 0.03 mgkg^{-1}. Propofol 12 mgkg^{-1}h^{-1} and alfentanil 0.07 mgkg^{-1}h^{-1} were started immediately after induction. Thereafter the infusion rates were adjusted as needed. Ventilation was with oxygen in air. BA was induced with thiopentone 4 mgkg^{-1} and fentanyl 3 µgkg^{-1} and maintained with isoflurane in nitrous oxide in oxygen and fentanyl 1.5 µgkg^{-1}h^{-1}. Vecuronium was used for muscle relaxation in both groups. Heart rate (HR), systolic (SAP) and diastolic (DAP) blood pressures were recorded at 5 min intervals. Antihypertensive treatment was given if SAP was >180 mmHg or DAP >110 mmHg over 15 min. Ephedrin was given if SAP was <100 mmHg. Central venous pressure was kept above 4 mmHg. Time interval from the discontinuation of anaesthetics to extubation was recorded. Recovery was assessed with Maddox wing apparatus and by scoring system hourly. Oxycodone and droperidol recquirements were recorded.

Results: Mean infusion rates for propofol and alfentanil were 10 (1.8) mgkg^{-1}h^{-1} and 70 (9) µgkg^{-1}h^{-1} respectively. Vecuronium 35(14) and 19(16) mgkg^{-1}h^{-1} was needed during TIVA and BA, resp.($p<0.05$). After induction of anaesthesia, HR, SAP and DAP were significantly higher in the BA group ($p<0.01$). Thereafter, SAP and DAP tended to be higher in the TIVA group, especially at the end of anaesthesia ($p<0.05$). No difference in HR was found between the groups. Two patients in the TIVA group needed antihypertensive therapy. Two patients in the TIVA and 3 patients in the BA group needed treatment for hypotension. There were no differences in the recovery parametres or oxycodone recquirements. Five patients in the BA and none in the TIVA group needed droperidol for nausea ($p<0.05$).

Discussion:: To control renal hypertension during TIVA, larger amounts of propofol and alfentanil were needed and slower recovery was observed than in previous studies in ASA 1-2 patients (3). Significantly more vecuronium was needed than with BA. TIVA had no clinical advantages over BA. Supplementation of TIVA with nitrous oxide could diminish the need for propofol and alfentanil leading to better recovery.

References::

1. Kirvelä et al. Br J Anaesth 1992; 68: 178-182
2. Chauvin et al. Anesth Analg 1987; 66: 53-56
3. Kay et al. Anaesthesia 1986; 41: 589-595

A.82

PREVENTION OF ACUTE TUBULAR NECROSIS BY VOLUME LOADING IN KIDNEY TRANSPLANTATION

Catherine Mouquet, Jacqueline Luciani,
Marc-Olivier Bitker, Pierre Viars.
Departments of Anaesthesiology and Urology
CHU Pitié - Salpêtrière, Paris, France.

Background and goal of study: Acute tubular necrosis (ATN) after kidney transplantation (KT) decreases the probability of graft's survival. The efficacy of volume loading (VL) in preventing ATN has been previously shown. (1) However, deleterious hemodynamic effects of VL have been reported in these high risk patients. (2) Accordingly, we investigated haemodynamic response to VL in chronic renal failure (CRF) patients during KT.

Patients and methods: 16 CRF patients, mean age 32 ± 8 yrs, who benefited from a KT, were studied. Heart rate (HR, bpm), mean arterial pulmonary pressure (MPAP, mmHg), capillary wedge pressure (CWP, mmHg) and cardiac output (CO, l.min^{-1}) measured using a Swan-Ganz catheter, and non invasive mean arterial pressure (MAP, mmHg) were measured before (CONT) and after induction (IND), before (PREX) and after (POSTX) the period of vessel clamping, at the end of surgery (END), and at the first postoperative day (D1). Data are mean ± SD.

Results : The mean VL during KT was 3950 ± 950 ml. Data are summarized in the table. Immediate diuresis after KT was observed in 100 % of the cases.

	CONT	IND	PREX	POSTX	END	D1
HR	75±12	70±12	66±10	70±10	72±14	84±12*
MAP	101±20	98±25	99±17	99±22	105±13	108±17*
MPAP	18±9	15±8	26±6*	29±8*	27±7*	25±8*
CWP	12±6	11±4	19±6*	22±8*	20±7*	14±7
CO	8.0±2.2	6.1±1.3	7.5±2.7	8.7±3.3	9.0±3.0	9.8±2.7*

Discussion : These results suggest that VL might be useful in preventing ATN. However VL may be associated with transient but significant increase in cardiac filling pressures. A pulmonary artery catheter monitoring appears useful to control the risk for an acute pulmonary edema in these high risk patients.

References : (1) Luciani J. et al Transplantation, 1979; 28, 308. (2) Cronnelly R. et al Anesthesiology 1983 ; 59, 49A.

A.83

VOLUME LOADING AND HORMONAL FACTORS IN THE PREVENTION OF ACUTE TUBULAR NECROSIS IN KIDNEY TRANSPLANTATION

Catherine Mouquet, Alain Carayon, François Clergue, Jacqueline Luciani, Marc Bitker, Pierre Viars.
Departments of Anaesthesiology, Urology and Biochemistry, CHU Pitié- Salpêtrière, Paris, France.

Background and goal of study : Acute tubular necrosis (ATN) after kidney transplantation (KT) has a deleterious effect on graft survival. The efficacy of volume loading (VL) in preventing this complication can be related to several mechanisms : increase in arterial pressure, graft's arterial blood flow, or atrial natriuretic factor (ANF). We measured ANF (pg.ml^{-1}), aldosterone, vasopressin (AVP, pg.ml^{-1}), and plasma renin activity (PRA, mg.ml^{-1}.h^{-1}) in 12 chronic renal failure patients before and after VL performed during KT.

Patients and methods : A Swan-Ganz catheter was used for measurements of cardiac filling pressures and cardiac output, and a radial artery catheter for arterial pressure. Haemodynamic measurements and blood samples were obtained before (CONT) and after induction (IND), before (PREX) and after (POSTX) the period of vessel clamping, and at the end of surgery (END). Hormonal dosages were determined by specific radioimmunoassays.

Results and discussion : VL induced a significant increase in both cardiac filling pressures and a further increase in ANF plasma levels, which were elevated at the preinduction state. PRA only increased at END without significant change in arterial pressure, probably due to furosemide administration. AVP increased after POSTX and END, without antidiuretic effect (Table).

	CONT	IND	PREX	POSTX	END
ANF	240±147	210±119	736±672*	669±439*	538±325
ALDO	206±329	162±119	203±177	216±141	167±96
PRA	1.9±1.8	1.8±1.7	1.9±1.7	2.8±2.1	3.5±2.9*
AVP	3.3±2.3	3.2±2.2	3.5±2.9	5.9±4.2*	14.9±17.5*

* $p < 0.05$ VS Cont.

All grafts had immediate diuresis and no ATN was noted.

Conclusion : The marked increase in ANF in response to VL suggests that the efficacy of VL in preventing ATN after KT may be related to natriuretic and diuretic effects of ANF and to its potent inhibitory effect on AVP.

A.84

IS THE VASOCONSTRICTIVE EFFECT OF CYCLOSPORINE MEDIATED BY ENDOTHELIN IN KIDNEY TRANSPLANTATION ?

Catherine Mouquet, Alain Carayon, Saïda Ourahma, Marc-Olivier Bitker, Pierre Viars.
Departments of Anaesthesiology, Urology and Biochemistry, CHU Pitié-Salpêtrière, Paris, France.

Background and goal of the study: Endothelin, a vasoconstrictive peptide synthetized by endothelial cells, has been implicated in the vasoconstritive effect of cyclosporine. (1) We measured plasma creatinine and endothelin (ET) levels before and after kidney transplantation (KT) in dialyzed chronic renal failure (CRF) patients to compare ET plasma levels and incidence of hypertension (HT) in patients treated vs non treated with cyclosporine.

Patients and methods: 53 CRF patients (19 women, 34 men), mean age 44 ± 12 yrs, undergoing KT were divided into 2 groups depending or whether or not they were treated with cyclosporine (CYCLO +, n = 22, (CYCLO -, n = 31). Plasma creatinine and ET by specific radioimmunoassay were measured before, 1 day, 1 and 3 months after KT in the 53 CRF patients, and in 20 healthy subjects, . Data are mean ± SD.

Results: Before KT : 26 (49 %) CRF patients were hypertensive. Plasma creatinine was 101 ± 32 mg.l^{-1}, and ET was higher than in healthy patients (5.9 ± 1.6 vs 3.6 ± 1.0 pg/ml^{-1}, $P<0.05$).

After KT : plasma creatinine and the incidence of HT (42 vs 41 %) were similar in both groups, although ET was higher in CYCLO + group (Table).

	Before KT	After KT	1 month	3 months
CYCLO -	5.8±1.2	6.6±1.8	3.8±0.8	3.7±0.8
CYCLO +	6.0±2.1	6.0.±1.4	4.3±0.9*	4.6±1.5*

* : $p < 0.05$ vs CYCLO -

Discussion: ET plasma levels are higher in CRF patients than in healthy patients. Although the improvement in renal function was similar in both groups, ET was higher in patients treated with cyclosporine, suggesting that the vasoconstrictive effect of cyclosporine may be mediated by ET, as previously suggested. (1) However, these higher ET plasma levels were not associated with an increased incidence of hypertension.

Reference: (1) Bunchan T.E. et al., Kidney Int., 1990; 37 : 365A.

A.85

RENAL BLOOD FLOW AND FUNCTION RELATIONSHIP IN RECENT RENAL TRANSPLANTATION IN MAN

L. Jacob, JJ. Chazalet, D. Payen, J. Bedrossian,
P. Teillac, B. Eurin

Department of Anesthesiology and Intensive care, Hôpital Universitaire Saint-Louis, Paris, France.

Renal Blood Flow (RBF) measurements may be of interest to predict renal allograft function (1). Duplex external Doppler ultra-sonography has been used in the identification and differential diagnosis of various causes of renal allograft dysfunction (2). With these techniques RBF value is not available since the artery diameter and the ultrasonic beam incidence angle are not known. Recent advance in Doppler technology, using miniaturized implantable microprobes (3), enables measurements of mean and phasic RBF supplying renal allograft in man. The goal of this study was to evaluate post-operative RBF and function relationship .

Material and methods. After informed consent and local ethical committee approval, 25 patients were studied after cadaveric renal transplantation. Patients were divided in two groups according to the initial function of the graft. Early function (Group I, n=13) was defined as daily urine output > 1000ml during the first 48 h, serum creatinine < 250 $\mu mol.l^{-1}$ at the end of the first week and no dialysis requirement. Group II patients (n=12) had delayed funtion. RBF was measured by pulsed Doppler implantable microprobe. Renal function was assessed by Urine output (Vu) and creatinine clearance (CrCl). **Protocol** Parameters were recorded at D0 and every day until the sixth post-operative day. **Statistical analysis** was performed using ANOVA and a Mann & Whitney test.

RESULTS are summarised in table 1 (Mean ± SD)

DISCUSSION: Renal hemodynamic study showed that : 1° RBFm at D0 was not predictive of the initial graft function. 2° RBFm decreased from D0 to D6 in GII. 3° Pourcelot index increased in both group and was significantly higher in GII suggesting a potent renal vasoconstriction in patients with delayed function.

REFERENCES: 1- Anderson et al Ann Surg 186;564,1977
2- Meyer et al Transplantation 50;974,1990
3- Payen et al Circulation 74;61,1986

Table 1 : Mean renal hemodynamic and function parameters in renal allograft with early (GI,n=13) and delayed(GII,n=12) graft function.*,¶ ; p<0,05 for intra and inter group comparison respctively.

	G	D0	D1	D3	D4	D6	ANOVA
RBFm	I	650	440	510	490	450	NS
		± 400	± 380	± 500	± 460	± 420	
	II	420*	320*	320*	330*	320*	0,05
		± 270	± 200	± 180	± 180	± 170	
RI	I	0,51	0,71*	0,72*	0,69*	0,69*	0,001
		± 0,14	± 0,21	± 0,19	± 0,16	± 0,19	
	II	0,63	0,73	0,88*¶	0,82	0,8	0,007
		± 0.2	± 0.22	± 0.14	± 0.17	± 0.23	
VU	I	14,3	6,5*	4*	3*	1,9*	0,0001
		± 6,5	± 3	± 1,5	± 1,3	± 0,5	
	II	2,8¶	1,7¶	1,6¶	1,4¶	1,1¶	0,25
		± 3,6	± 1,5	± 1,8	± 1,3	± 0,9	
CR CL	I	37,4	34,9	44,5	45,7	41,6	NS
		± 40,3	± 21,1	± 21,7	± 19,3	± 15,4	
	II	9,2¶	6,8¶	6,1¶	9¶	8,2¶	NS
		± 9.4	± 5.8	± 6	± 9,3	7,6	

A.86

EFFECT OF RECOMBINANT HUMAN GROWTH HORMONE (HGH) ON PROTEIN METABOLISM IN SURGICAL PATIENTS

F Carli, J Anderson, M Read, D Halliday

Department of Anaesthesia and Nutrition Research Group, Northwick Park Hospital and Clinical Research Centre, Harrow, England

Background and goal of the study: The metabolic response to surgery include weight loss and negative nitrogen balance.

We have investigated the possibility of using anabolic stimuli in combination with low nitrogen/calorie intake to attenuate net protein breakdown and promote body nitrogen retention.

Materials and metods: Sixteen patients undergoing colorectal surgery for excision of tumour were studied. Daily nutritional intake, based on nitrogen 0.1 g kg^{-1} and calories 84 J kg^{-1} was started orally 6 days before surgery and continued parenterally for 6 days after operation. One group (control, n=8) received placebo whilst the other group (HCG, n=8) received a daily s.c. dose of 0.15 IU kg^{-1} of recombinant human growth hormone for 6 postoperative days. Urinary excretion of nitrogen was measured before surgery and for 6 consecutive days after operation. Quadriceps muscle mixed protein synthetic rate was extimated in eight patients using stable isotope L(1-^{13}C) leucine before and 6 days after surgery.

Results and discussion: Urinary nitrogen excretion increased after surgery in both groups, however, the cumulative nitrogen excretion was significantly attenuated in the HGH group compared with the control group (p=0.017). Protein synthetic rate (% h^{-1}) in the quadriceps muscle decreased by 25% in the control group after 6 post operative days, whilst it increased from a mean value of 0.03014 (SD, 0.0063) to 0.042094 (SD, 0.013) in the HGH group. These findings indicate a modulatory role of HGH on protein synthesis and breakdown in stressed patients receiving a hypocaloric nutrition.

A.87

GLYCINE AND ITS METABOLITES DURING AND AFTER INTRAUTERINE YAG LASER SURGERY

M.J. Van Boven, MD, P.E. Pendeville, MD and F.J. Singelyn, MD.

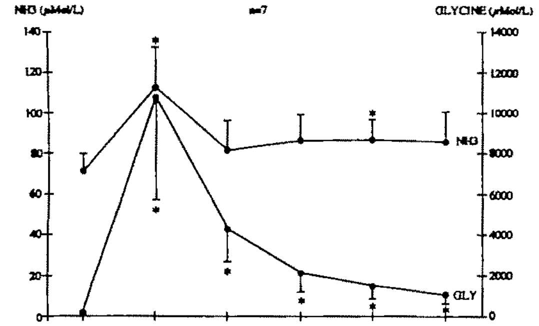
Dept of Anesthesiology, St Luc Hospital, UCL Medical School,
1200 Brussels, Belgium.

Glycine 1.5% solution is used as a distending medium during intrauterine YAG laser surgery (IYAGLS). Very high amounts of glycine solution may be resorbed during the procedure leading to fluid overload, electrolyte dilution and hyperglycinemia. The aim of this study was to determine the levels of glycine and its metabolites during and after IYAGLS.

Methods: After informed consent, seven ASA I-II, artificially menopaused patients were included in this study.IYAGLS was performed under general anesthesia. Intravenous fluid was restricted to 500 ml of Ringer's lactate during the induction period followed by 2 ml $\mathrm{kg}^{-1}\mathrm{h}^{-1}$during and after the procedure. The in and out fluid irrigating fluid balance was monitored by a volumetric technique.Intrauterine pressure was monitored by a pressure transducer connected to the hysteroscope.Hematocrit, serum osmolarity, sodium, potassium chloride, proteins, aminoacids and ammonia (1) were determined before and 30, 60, 120, 180 and 240 minutes after the beginning of the procedure. Oxaliuria was assessed on two 12 hours urine collections taken before and after IYAGLS (2). A Wilcoxon signed rank test was used in order to analyse the biological parameters. Results are expressed as means ± SEM.

Results: Mean irrigant absorption was 1128±254,5ml. Duration of the procedure was 29,7±6,3 minutes. Mean intrauterine pressure was 165±17 mm hg. Serum concentrations of glycine and ammonia are presented in fig 1.

fig.1



Glycine serum concentrations increase massively reaching a 50 (4-100) times the initial values after 30 minutes. Ammonia serum concentrations increase moderately. There is no significant cha in the other studied parameters.No hyperoxaliuria was found the procedure.There is no correlation between glycine serum concentration and infusion pressure or resection time. No symptoms of glycine toxicity were noted.

Conclusion: Massive irrigant absorption may occur during IYAGLS. Beside the risk of fluid overload, glycine absorption may lead to hyperglycinemia and hyperammoniemia (3). As general anesthesia may mask the early signs of glycine overload, we recommend to perform IYAGLS under regional anesthesia and to ensure a good washout of the uterine cavity during the procedure to avoid overpressure.

References: 1. Can J Anaesth 38, 1: 90-97, 1991.
2. Br J Urol 53: 250-252, 1981.
3. Anesthesiology 58: 577-579, 1983.

A.88

CARBOHYDRATE DEFICIENT TRANSFERRIN: A NEW COPREDICTOR OF ALCOHOLISM RELATED POSTOPERATIVE COMPLICATIONS?

*T.Hell, *C.Spies, *T.Neumann, §C.Müller

*Department of Anesthesia and Intensive Care, Steglitz
Medical Center, §Department of Clinical Chemistry and
Biochemistry, Rudolf Virchow Medical Center,
Free University of Berlin, Berlin, Germany

Alcohol dependent patients are at risk for increased morbidity during ICU therapy. Since post-OP alcohol withdrawal syndrome (AWS) may induce severe complications, sensitive preoperative evaluation of physical dependence is mandatory. Compared with other conventional parameters (MCV,GGT,ASAT,ALAT) elevated Carbohydrate deficient transferrin (CDT), an isoform of tranferrin, is reported to be a reliable marker[1] of chronic alcohol abuse (50-70 g/d). We investigated whether pre-OP diagnosis of dependence can be improved by determination of CDT.

Fifty male patients with a history of alcohol consumption underwent resection of oropharyngeal laryngeal or oesophageal tumors with subsequent ICU management. Precise history was supplemented by alcoholism-associated questionnaire[2], conventional lab tests (MCV,GGT,ASAT, ALAT) and determination of CDT performed by micro-anion-exchange-chromatography[3] (nl<9mg/l). The pre-OP assessment was validated by occurrence of post-OP withdrawal symptoms. Statistical analysis was performed by MANOVA.

Preoperatively 11 patients were diagnosed as dependent, 13 patients developed post-OP AWS. 15 patients were preoperatively diagnosed as chronic abusers without physical dependence. All dependent patients had elevated CDT (> 9mg/l) except for one. In contrast, no patients who were sober for more than seven days had abnormal CDT levels (fig.1).

CDT can be used as sensitive parameter for chronic alcohol abuse and as reliable copredictor for the occurrence of alcoholism related postoperative complications.

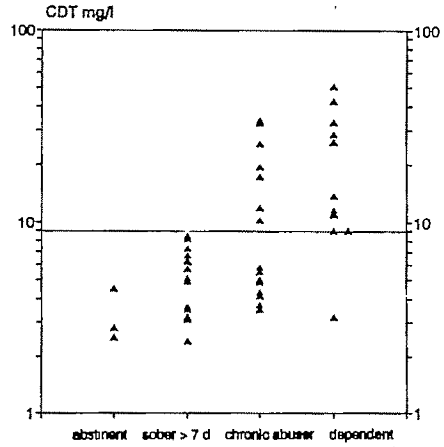


Fig. 1: CDT values in different groups (pathological CDT > 9mg/l)

References: 1. Clin. Chem. 12:2029-37, 1991, 2. JAMA 259 :51-54, 1988, 3. Lab Med 15:278, 1991

A.89

EFFECTS OF DIAZEPAM ADDITIVES ON THE MONONUCLEAR PHAGOCYTIC SYSTEM

Catalá JC, Carrera JA, Iribarren MJ,
García Pedrajas F, Arroyo JL

Department of Anaesthesiology, Clínica Universitaria, School of Medicine, University of Navarra, Pamplona, Spain

Introduction:

In previous studies we dealt with the possibility that diazepam may reduce the expression of vimentin filaments, phagocytic activity, and the membrane display of HLA DR molecules in human monocytes. In the present in vitro study we have evaluated the possible contribution on these effects of additives contained in diazepam solution (propylene glycol, ethanol and benzyl alcohol) on the expression of vimentin filaments, the phagocytic activity, and the membrane display of HLA DR molecules in human monocytes.

Methods:

The study was performed on centrel blood samples from healthy donnors.

Blood samples were divided into four fractions: three blood aliquots were incubated with additive mixture of diazepam (0.4 mg.10^{-6} monocytes) for 1, 2, and 16 hours. Also, control aliquots were incubated with no additives for 0 (basal, 1, 2, and 16 hours) .

After isolation of human monocytes by the Boyum technique, the membrane display of DR molecules, the expression of immunoreactive vimentin filaments, and the latex particles phagocytosis index were analized by immunofluorescence using monoclonal antibodies.

Results:

All parameter determined decreased significantly ($p<0.01$) after incubation with diazepam additives, and no variations were reported in control monocytes at basal time and at different times.

Additives were found to be strong inhibitors of expression of vimentin filaments, phagocytic activity, and the membrane display of HLA DR molecules after 1, 2, and 16 hours. Although the decrease of this values was of lower magnitud after 16 hours (see Table below). Therefore, we must take into account that the higest diazepam doses administered, the highest doses of additives are given.

Conclusions:

Diazepam additives produce in vtro disfuction of the mononuclear phagocytic system.

	HLA DR	FAG LATEX	F. VIMENTINA
BASAL	75.2±8.4	68.2±5.5	75.7±10.2
1ª HORA	57.8± 10.2**	51.5±10.4**	58.0±13.1**
2 HORAS	50.7±9.2**	47.0±9.9**	51.0±10.2**
16 HORAS	59.0±19.6**	56.5±12.5**	58.2±14.8**

References: Morisaki H, et al: Br J Anesth 1991; 66: 97-102.

A.90

Adrenocortical Function: A Clinical Comparison of Etomidat-Lipuro® and Hypnomidate®

Wiebalck A[*], Vanacker B, Van Aken H, Sermeus L, Bouillon R[**], Amery A[***]
Department of Anesthesiology, University Hospitals, Katholieke Universiteit Leuven, Belgium

Goal: The comparison of the two preparations of etomidate in terms of endocrinological changes after induction of anesthesia with Etomidat-Lipuro®, Hypnomidate® and Diprivan® as a control.

Materials and Methods: All 30 patients belonged to group 1 or 2 referring to the ASA classification and underwent minor surgery. They were allocated at random to one of the 3 induction agents. A radial artery catheter was inserted in every patient. Sampling took place 30 min before and 1 and 2 h after induction. Additional samples were drawn 30 min, 1, 2 and 22 hours after iv administration of 0,25 mg ACTH (Synacthen®, Ciba-Geigy). The plasma concentration of cortisol, 17a-OH-progesterone, aldosterone as well as the activity of renin was determined by HPLC (High Performance Liquid Chromatography).

Results and Discussion: Cortisol levels were depressed initially by all the hypnotic drugs used. While there was a spontaneous recuperation in the Diprivan® group after 2 hours combined with a positive overshooting response to ACTH stimulation, cortisol in the etomidate groups could not be stimulated. This phenomenon can be explained by the blockade of the 11-ß-hydroxylase (1). Cortisol normalized slowly during the following 24 hours. The 17a-OH-progesterone increase was significant in the etomidate groups after the administration of ACTH. The aldosterone level decreased after etomidate injection and did not normalize 24 hours later while there was a normal response to ACTH in the propofol group. There was a normal decrease of renin activity in the three groups after the administration of ACTH.

Conclusion: Cortisol and aldosterone are depressed by both etomidate preparations, but the clinical relevance is minimal in a normal patient after a single bolus injection (2).

References:

1. Crozier TA et al. Endocrinological changes following etomidate, midazolam, or methohexital for minor surgery. Anesthesiology (1987) 66:628-635
2. Stuttmann R et al. Etomidate versus Etomidate und Hydrocortison zur Narkoseeinleitung bei abdominal-chirurgischen Eingriffen. Anaesthesist (1988) 37:576-582

---

[*] Institut für Anästhesiologie und Operative Intensivmedizin Mannheim, Universität Heidelberg, Germany

[**] Department of Endocrinology, KU Leuven, Belgium

[***] Department of Cardiology KU Leuven, Belgium

A.91

ISOFLURANE INHIBITS Ca^{2+}-INDUCED INSULIN SECRETION FROM ELECTRICALLY PERMEABILISED ISLETS OF LANGERHANS

JP Desborough, PM Jones, SJ Persaud, SL Howell

Biomedical Sciences Division, King's College London,
Campden Hill Road, London W8 7AH, U.K.

Introduction: Isoflurane, like halothane and enflurane, inhibits glucose-induced insulin secretion from isolated rat pancreatic islets of Langerhans (1). Following metabolism of glucose inside islet B cells, generation of intracellular regulators, including Ca^{2+}, leads to activation of protein kinases and exocytosis of insulin. The mechanism by which volatile anaesthetics inhibit the stimulus-secretion pathway in pancreatic B cells has not been elucidated. We have studied the effects of isoflurane on insulin secretion from islets in which the cells have been permeabilised by high voltage discharge to allow the introduction of ions and small molecules into the intracellular compartment.

Methods: Islets were isolated by collagenase digestion of the pancreas and preincubated in a bicarbonate buffered medium at pH 7.4 for 30-60 min.The islets were washed in a permeation buffer with $CaCl_2$ added to produce a free Ca^{2+} concentration of 50 nM, and permeabilised by five exposures to an electric field of 3.4kV/cm (2). Reservoirs of buffer were equilibrated with O_2 (100%) or with O_2 and isoflurane 2%. Groups of five islets were then incubated at 37°C for 30 min in 0.5 ml permeation buffer containing 50nM- or 10μM-Ca^{2+}, with or without isoflurane. Insulin content in samples of buffer was measured by radioimmunoassay.

	Insulin secretion (mean ± SE) pg / islet / 30min n=9
Ca^{2+} 50 nM	98 ± 11
Ca^{2+} 50 nM + isoflurane	71 ± 5
Ca^{2+} 10 μM	150 ±15
Ca^{2+} 10 μM + isoflurane	95 ± 5

Discussion: Isoflurane inhibition of insulin secretion from permeabilised islets in the presence of a maximum stimulatory concentration of Ca^{2+} (10μM) suggests that isoflurane impairs the ability of the B cells to respond to Ca^{2+}. It is likely therefore that isoflurane acts at a stage in the secretory pathway beyond changes in intracellular Ca^{2+}.

References

1. JP Desborough, PM Jones, SJ Persaud, MJ Landon, SL Howell. Br. J. Anaes. 1992; 69: 532P.
2. PM Jones, J Stutchfield, SL Howell. FEBS Lett. 1985; 191: 102-106.

A.92

EXERCISE AND MALIGNANT HYPERTHERMIA: FAMILY INVESTIGATIONS.

G KOZAK RIBBENS*, L RODET*,
J BORSARELLI***, M AUBERT** and PJ COZZONE*.
* CRMBM- URA CNRS 1186, Faculté de médecine, 13005-MARSEILLE; ** DAR, HIA LAVERAN, 13398-MARSEILLE ARMEES; *** DAR CHU, Hopital de la Timone, 13005 - MARSEILLE.

"Exercise Hyperthermia" (EH) is diagnosed when an exercising subject suffers concomitantly of mental confusion, hyperthermia above 40°5 C and rhabdomyolysis. A number of similarities have been observed between malignant and exercise hyperthermia symptoms and the pre-existence of a muscular disorder has been hypothetized in EH patients.

We have systemically investigated 60 patients with EH or exercise myolysis in the same way as patients with malignant hyperthermia (MH) syndrome, using non-invasive techniques (P31-NMR), contracture tests on biopsies according to the European Malignant Hyperpyrexia Group (EMHG) protocol (1) and morphological and biochemical examinations of the muscle fibers.

We report here the results of investigations which were conducted in the families of 3 EH patients, one of them died during the EH episode. According the EMHG classification, these 2 patients were found MH susceptible (MHS) with halothane and caffeine positive contracture tests. P31 NMR spectroscopy revealed an abnormal profile of muscular energetic metabolism, particularly when the exercise was conducted under partial ischemia with the application of a tourniquet.

Among the family members, MHS subjects were discovered. In some families, a link between MH and EH could be shown.

1- European Malignant Hyperpyrexia Group, ELLIS et al., Br. J. Anaesth. , 1984, 56, 1267-1269.

This work was supported by grants of APM (Assistance Publique à Marseille), AFM (Association Française contre le Myopathies), EMHA (European Malignant Hyperthermia Association), CNRS (Centre National de la Recherche Scientifique) and DRSSA (Direction de la Recherche du Service de Santé des Armées).

A.93

IS BURKITT'S LYMPHOMA AN ETIOLOGY OR A DIFFERENTIAL DIAGNOSIS OF MALIGNANT HYPERTHERMIA?

Lienhart A, Deriaz H, Desnault H, Masini JP, Delva E

Department of Anaesthesia and Intensive Care,
Saint Antoine Hospital, Paris, France

Association between Malignant Hyperthermia (MH) and Burkitt's lymphoma (BL) is occasionnally reported,[1,2] and generally considered as coincidental.[3,4] Nevertheless,the hypermetabolic crisis might not be MH.

Case 1: A 46 yr-old man was anaesthetized in 1986 with thiopental, pancuronium, ethrane and N_2O in O_2, for an exploratory laparotomy. A poor relaxation was noted, then a ventricular arrhythmia. A 9.2 mmol/l hyperkaliemia was associated with a severe acidosis (pH 6.90, $PaCO_2$ 81.5 mmHg) and a hyperpyrexia (39.5 °C). CPK remained within a normal range (69 IU). The patient died few hours later despite intensive cooling, alkalinization and dantrolene administration. A diagnosis of BL was made from tissue biopsy of a very large tumor.

Case 2: A 30 yr-old man was anaesthetized in 1992 with thiopental, atracurium, ethrane and N_2O in O_2, for an exploratory laparotomy. Within 15 min $P_{ET}CO_2$ increased from 44 to 57 mmHg. With dantrolene and a 20 l/min ventilation, $PaCO_2$ was 45 mmHg ($P_{ET}CO_2$ 42 mmHg), pH 7.10, bicarbonate 14 mmol/l, lactate 3.2 mmol/l, CPK 21 IU. Surgery was delayed and postanaesthetic hyperventilation was required to avoid hypercapnia. Two days later the laparotomy was performed and a very extensive tumor was discovered, of Burkitt's type. During and after surgery, the rectal temperature was 0.5 °C higher than the esophageal one. Postoperatively oxygen saturation was lower in the mixed venous blood than in the femoral vein. Dantrolene was discontinued; administration of corticosteroids and cyclophosphamide was followed by a rapid fall in temperature from 39.9 to 37 °C and a dramatic decrease in ventilatory requirement. Two weeks later a muscle biopsy was taken and *in vitro* contracture tests were performed: the phenotype was MHN. A second chemotherapy was induced, followed by an intense antitumor response. The patient died one month later, from septic complications of aplasia.

Discussion: More than 200,000 anaesthesia have been performed in our institution since 1984. We observed only these two cases of severe MH. A pure coincidence is very unlikely, since MH has been previously reported in association with BL,[1,2] not with other more common malignancies.[3] The normal *in vitro* contracture tests in one patient, and the normal CPK level in the two patients, suggest that the hypermetabolic crisis was not MH, but a severe disorder mimicing MH, related to the tumor itself. Corticosteroids and cyclophosphamide might be a more appropriate treatment than dantrolene alone.

References: 1. Tsueda K. Anesth Analg 57:511, 1978
2. Lees DE. Anesth Analg 59:514, 1980
3. Brownell AKW. Br J Anaesth 60:303, 1988
4. Kaplan RF. Ann ASA Refresher Course 1991

A.94

INHIBITION OF INCREASE OF BLOOD THROMBOXANE CONCENTRATION BY ACETYLSALICYLIC ACID AFTER RELEASE OF TOURNIQUET IN LOWER EXTREMITY OPERATIONS

Raimo Ojanen, Seppo Kaukinen, Erkki Seppälä,
Liisa Kaukinen and Heikki Vapaatalo

Dept Anaesthesia, University Hospital and
Dept Biomedical Sciences, Tampere University,
Tampere, Finland

Background and goal of study: Ischaemia stimulates (TxA_2) synthesis. TxA_2 is a powerful aggregator of platelets and a vasoconstrictor. Tourniquet used in operations in extremities is a risk factor for thromboembolic complications. The metabolic products of arachidonic acid , e.g. TxA_2 may contribute to this. The inhibitor of TxA_2-synthesis given before placement of tourniquet probably would prevent the release of TxA_2 and harmful effects caused by it.

Material and methods: 32 generally healthy patients undergoing to orthopedic operations requiring tourniquet were studied. The patients were divided into four groups of eight patients. Three groups received acetylsalicylic acid (ASA) 25, 100, 500 mg p.o. three hours before operation in order to inhibit TxA_2 synthesis. The control group did not receive any drug for this purpose. The patients were anaesthetized using enflurane as a main anaesthetic agent. After induction of anaesthesia catheters were introduced into the radial artery and femoral vein in the extremity to be operated on. Blood samples for determination of serum and plasma TxB_2 concentrations were withdrawn simultaneously from artery and vein after the induction of anaesthesia and 3, 10, 30, 60 and 120 minutes after the release of tourniquet. Because TxA_2 disappears very fast, its metabolite TxB_2 was measured. It was determined using RIA.

Results and discussion: In the control group serum TxB_2 concentrations (S-TxB_2) increased distinctly after the release of tourniquet: 40.0 + 20.0 (SEM) - 73.5 + 39.0 ng/ml. The concentrations were at the highest at 60 minutes. In the patients received ASA 25 mg the base line of S-TxB_2 was lower than in the control group (17.0 +5.0 ng/ml), but this dose of ASA did not inhibit the increase of S-TxB_2 after release of tourniquet. The base line of S-TxB_2 in patients received ASA 100 mg was 1.9 + 0.6 ng/ml, and respectively in ASA 500 mg patients it was almost zero. Both these doses of ASA prevented the increase of S-TxB_2 after the release of tourniquet. Radial artery concentrations of S-TxB_2 behaved as venous concentrations.

Conclusions: 100 mg ASA p.o. is probably enough to prevent possible harmful effects caused by TxA_2 when tourniquet is used.

A.95

THE COMBINED PROPHYLACTIC ADMINISTRATION OF H1 AND H2 RECEPTOR BLOCKERS IN THE PREVENTION OF PROTAMINE RELATED HAEMODYNAMIC EFFECTS AND THE RELATION BETWEEN ANTIHISTAMINICS - LEUCOCYTES AND PULMONARY VASCULAR RESISTANCE

Durak P, Özgök A, Esen H, Erdemli Ö, Ebil S

Department of Anaesthesiology, Turkish High Advanced Hospital, Ankara, Turkey

Background and goal of study: We studied the combined prophylactic administration of H1 and H2 receptor blockers in the prevention of protamine-related haemodynamic effects.

Materials and methods: 30 patients subjected to coronary artery surgery were assigned to two groups. Patients in group I (n=15) received 50 mg Ranitidin-HCl iv after anaesthetic induction followed by 50 mg Chlorphenoxamin HCl into the cardiopulmonary bypass pump circuit during rewarming. The patients in group II (n=15) served as controls and had no treatment. The same format of anaesthesia was provided to all patients and consisted of fentanyl-diazepam-pancuronium. In both groups, the same amounts/kg of heparin and protamine sulphate were used for anticoagulation and reversal of heparin effects respectively. Systemic and pulmonary haemodynamics, haemogram and ionized serum-Ca were followed.

Results and discussion: In the control group, protamine induced significant decreases in systolic and mean arterial pressures (SAP $p<0.01$, MAP $p<0.05$) at 1 min and in diastolic arterial pressure ($p<0.05$) at 5 min. Ten min after protamine, serum leucocyte count was significantly decreased in the control group ($p<0.05$). There was also a significant negative correlation between pulmonary vascular resistance (PVR) and serum leucocyte count 5 min after protamine ($r=-0.85$). In group I, the administration of Ranitidine and Chlorphenoxamin prevented the haemodynamic changes observed in the control group whereas we did not observe any modification of the relationship between PVR and serum leucocyte counts.

References: Kamban J, Meszaros R, Mennill W, Stewart J, Smith B, Bender H: Prophylactic administration of Histamine 1 and Histamine 2 Receptor Blockers in the Prevention of Protamine-related Haemodynamic Effects. Can J Anaesth 1990; 37:420-426.

A.96

THE RELATIONSHIP BETWEEN CARDIOPULMONARY BYPASS RELATED IMMUNOLOGIC EFFECTS AND COMPLEMENT, THROMBOXANE AND LEUCOCYTE PARAMETERS

Durak P, Özgök A, Saydam G, Türkmen A, Erdemli Ö, Ebil S

Department of Anaesthesiology, The Higher Specialization Hospital of Turkey, Ankar, Turkey

Backgound and goal of study: Our aim was to study immunological reactions related to cardiopulmonary bypass and protamine administration in patients undergoing coronary bypass surgery. For this purpose we followed plasma levels of complement ((C3), (C4) and (C5)), thromboxane B2 (TrxB2) and leucocyte counts.

Materials and methods: Twenty patients scheduled for coronary bypass surgery were subjected to general total intravenous anaesthesia with fentanyl-diazepam-pancuronium after morphine (10 mg) and diazepam (10 mg) premedication. Anticoagulation was provided with heparin, 4 mg/kg and all patients were reversed with the same amount/kg of protamine sulphate administered over 10 min via a central vein. Blood samples were taken along with haemodynamic measurements after anaesthetic induction and immediately before, and 10 min after protamine infusion, for measurements of TrxB2, (C3), (C4), (C5), arterial blood gases and total blood cell counts. Both arterial and central venous cell counts were obtained at each measurement period. Student´s T-test was used for the statistical analyses.

Results and discusssion: A significant increase of venous leucocyte count ($p<0.01$) which correlated with TrxB2 ($p<0.05$) was observed after protamine. In addition platelet count decreased significantly after protamine ($p<0.05$). (C3), (C4) and (C5) increased significantly ($p<0.01$ respectively) during cardiopulmonary bypass.

Conclusions: We conclude that leucocyte count and TrxB2 can be used to identify protamine-related reactions and that (C3), (C4) and (C5) could identify immunological reactions during cardiopulmonary bypass.

Reference: Morel D, Zapol W, Thomas W, Thomas S: C5a and Tromboxane Generation Associated with Pulmonary Vaso- and Bronchoconstriction During Protamine Reversal of Heparin. Anesthesiology 1987; 66:597-602.

A.97

USE OF APROTININE DURING CYTOREDUCTIVE SURGERY OF OVARIAN CANCER

F. Lequeau, JL Bourgain, D. Castaigne, M. Samama

Department of Anesthesiology and Surgery, IGR, Villejuif and Department of Anesthesiology Hôpital Pitié Salpêtrière, Paris, France

Background : Cytoreductive surgery is often the first part of the treatment of ovarian cancer. This surgery is associated with major blood loss. The presence of Plasminogen activating factor has been reported in ovarian cancer cells. The aim of this study was to evaluate possible per-operative coagulation disorders in a control group and to test the efficacy of aprotinine infusion in the reduction of bleeding and correction of coagulation disorders during surgery.

Methods : Twenty one consecutive patients with ovarian cancer scheduled for cytoreductive surgery were included. The ten first patients being the control group, the following 11 patients received aprotinine 2 M.UK as a loading dose and 500 000 UK/hr up to 2 hours after surgery. Both groups received a standardized induction (etomidate 0.3 mg/kg, fentanyl 4 mcg/kg, vecuronium 0.1 mg/kg). Anaesthesia was maintained by isoflurane and intermittent injection of fentanyl and vecuronium. Coagulation tests were performed before and at the end of surgery. Blood loss was measured by the volume of aspirated blood and by weighing surgical swabs. In the post operative period, particular attention was given to the detection of phlebitis. In the case of respiratory symptoms, pulmonary angiography was performed to exclude pulmonary emboli. Results are expressed as mean (SD). Unpaired t-test was used for statistical analysis.

Results : As expected, ovarian surgery was associated with severe coagulation disorders. Although fibrinogen concentration and platelet count were significantly higher in aprotinine group, blood loss and blood replacement were similar in the two groups. Phlebitis was diagnosed in one case and no pulmonary emboli was detected in 5 patients with respiratory symptoms (aprotinine group).

Conclusion : Severe coagulation disorders are present during ovarian cytoreductive surgery ; a random study is necessary to confirm the beneficial effects of aprotinine.

Table 1 :

	Control group	**Aprotinine**
Age (yrs)	54 (10)	49 (12)
Blood loss(g)	5890 (3780)	5310 (3730)
Redcell pack(g)	2190 (1290)	1950 (1890)
Fresh frozen P(g)	1080 (440)	441 (670)
Quick time (%)	48 (17)	51 (14)
Platelets/mm x 1000	3127 (59)	235 (81)*
Fibrinogen(g/l)	1.08 (0.45)	1.59 (0.52)*

m (SD) * $p < 0.05$

A.98

BLOOD REQUIREMENTS REDUCTION IN ORTHOTOPIC LIVER TRANSPLANTATION WITH APROTININ.

Monedero P, Carrera J, Catalá J, Carrascosa F, Arroyo JL.

Anesthesiology Department. Clínica Universitaria. School of Medicine. University of Navarra. Pamplona. Spain.

Introduction: Hiperfibrinolysis seems to be an important cause of intra- and postoperative bleeding in patients undergoing orthotopic liver tranplantation (OLT). Aprotinin is an inhibitor of human plasmin and kallikrein that theoretically can inhibit the development of fibrinolysis. Aprotinin has proved to be useful in reducing operative bleeding in cardiac surgery (1) and there are good preliminary results in OLT (2). We have performed a retrospective study to evaluate the effect of aprotinin on hemostatic parameters and intraoperative requirements of blood derivates in 16 patients who underwent OLT. Results were compared with a historical group of 19 untreated patients.

Methods: Treated patients (n=16) received aprotinin as a bolus of 2 million kallikrein inactivator units (KIU) at induction, followed by a maintenance dose of 500000 KIU/h until the end of surgery. Standard clotting tests were performed and the total amount of blood derivatives infused intraoperatively was also measured.

Results: There were no significant differences between groups in preoperative diagnosis, Child-Pugh status and hemostatic variables.

In patients undergoing OLT, aprotinin significantly reduced ($p<0.05$) packed RBC (1620 ± 810 ml vs 4260 ± 3570 ml), fresh frozen plasma (2670 ± 870 ml vs 4710 ± 2130 ml), platelets (4.6 ± 5.5 units vs 10.3 ± 8.4 units), cryoprecipitates and albumin requirements as compared with untreated patients. Additionally, aprotinin reduced the usual increase in the D-dimer levels and the decreased alpha-2-antiplasmin during the anhepatic and postanhepatic periods, as compared to untreated patients.

Conclusions: We conclude that aprotinin is a highly effective treatment of intraoperative bleeding in patients undergoing OLT. Reduction of increased fibrinolysis seems to contribute to this effect.

References:

1. Bidstrup BP, et al: Reduction in blood loss and blood use after cardiopulmonary bypass with high dose aprotinin (Trasylol). J Thorac Cardiovasc Surg 1990; 97: 364-72.
2. Grose H, et al: The use of high dose aprotinin in liver transplantation: the influence on fibrinolysis and blood loss. Thromb Res 1991; 101: 968-972.

A.99

HIGH DOSE APROTININ VERSUS DESMO-PRESSIN ACETATE TREATMENT IN CARDIAC SURGERY.

Hidalgo F, Páramo JA, Catalá JC, Carrascosa F, Monedero P.
Anesthesiology and Hematology Departments.
Clínica Universitaria. School of Medicine. University of Navarra. Pamplona. Spain.

Introduction

It has been suggested that platelet dysfunction and hyperfibrinolysis are a major cause of the hemostatic defect associated with cardiopulmonary bypass (CPB). Increased blood loss is the most obvious clinical manifestation reflecting this defect.

The aim of this study was to evaluate the influence of the administration of aprotinin and DDAVP in the prevention of bleeding after CPB.

Methods

This study included 124 patients, of which 110 accomplished the study, randomized into the following groups: Group A (n=28) treated with aprotinin 2×10^6 KIU immediately after anesthetic induction, 2×10^6 KIU in the extracorporeal circuit and 0.5×10^6 KIU/h until the end of surgery; group B (n=26) received DDAVP perfusion (0.3 µg/kg in 20 minutes) started after protamine neutralization; group C (n=28) were treated with DDAVP (0.3 µg/kg) as in group B and an additional dose 6 hours after surgery; and group D (n=28) wich not receive any treatment.

Postoperative blood loss and blood requirement was measured. Some fibrinolysis parameters and other coagulation parameters were studied before, during and after surgery.

Results

There was a significant reduction in postoperative bleeding and blood requirements in group A as compared to groups B, C and D (table I). Whereas no differences in the analyzed parameters were observed in both DDAVP treated groups with respect to the untreated group, we found a significant reduction of a2-antiplasmin consumption (p<0.02) and of fibrin degradation products generation (p<0.001) in the aprotinin group.

	A	B	C	D
Blood loss (ml/m2)	135.8±156.3**	551.8±324.1	498.5±235.6	438.7±228.1
Homologous blood requirement (ml/m2)	366.1±331.9*	740.4±416.3	662.8±380.7	678.0±380.7

A vs B-C-D: **=p<0.004; *= p< 0.02

Conclusions

We conclude that aprotinin offers a better alternative than DDAVP in the prevention of bleeding after CPB surgery and this effect is clearly related to a reduction of fibrinolysis.

References: 1. Bidstrup BP, et al. Reduction in blood loss and blood use after cardiopulmonary bypass whith high dose aprotinin (Trasylol). Blood 1990, 76:1680-97. 2. Rocha E, et al. Does desmopressin acetate reduce blood loss after surgery in patients on cardiopulmonary bypass?. J Thorac Cardiovasc Surg 1990, 97: 364-72.

A.100

Aprotinin does not decrease surgical bleeding and could promote arterial thrombosis in the pig: A prospective randomized, blind, study.

ChM. Samama[1], E. Mazoyer[2], P Bruneval[3], Ph. Bonnin[4], M. Bonneau[5], G. Pignaud[2], P. Viars[1], JP. Caen[2], LO.Drouet.[2]
1: Département d'Anesthésie, Hopital Pitié, Paris -2: INSERM U 353, IVS, Paris -3: Département d'Anatomo-Pathologie, Hopital Broussais, Paris -4: Laboratoire d'Explorations fonctionnelles, Hopital Lariboisière, Paris -5: INRA, Jouy, France

Hemostatic properties of aprotinin could be counterbalanced by an increased risk of thrombosis. A randomized, blind study was conducted to consider the potential thrombogenicity of aprotinin, using the Folts' model on femoral arteries in 12 pigs. The flow variations were measured by a pulsed Doppler in anesthetized animals. The spleen was exposed and the very distal extremity was injured for splenic bleeding. Ear immersion bleeding time was performed. During the first part of the study, a stenosis was performed succcessively on both femoral arteries, each for a period of 30 min, without prior injury, to assess the integrity of the vessel, and to check that the arteries did not develop spontaneous cyclic flow reductions (CFR), permanent cessation of flow (PCF) or partial thrombosis, when a stenosis is applied. Then the clamp was released and a bolus of placebo (saline), or aprotinin (4 millions KIU, followed by a continuous infusion of 1 million KIU.hr^{-1}), was administered. At the end of the bolus, the second part of the study began. Stenosis was applied to the arteries. If CRF, PCF, or partial thrombosis were observed, without prior injury, then the infused drug (aprotinin or saline) was considered a prothrombotic drug, and the opposite artery was studied. For each animal, right and left femoral artery segments were fixed and studied (morphologic study). Eighteen arteries were studied. In the aprotinin group, 6 arteries out of 8 developped an unexpected spontaneous thrombosis, as compared with only 2 out of 10 arteries in the control group (p=0,02). The morphologic study confirmed the occcurence of thrombosis in 4 normal arteries out of 7 studied, as compared with only 1 out of 8 in the control group. The splenic bleeding time and the ear immersion bleeding time were not different from one group to another. No difference could be evidenced with regard to the values of activated partial thromboplastin time, prothrombin time and fibrinogen. Aprotinin did not reduce the surgical bleeding but it could promote the developpement of arterial thrombosis in the pig.

A.101

EFFECTS OF RECOMBINANT-HUMAN ERYTHROPOIETIN ON POSTOPERATIVE TRANSFUSION REQUIREMENTS IN SUBJECTS UNDERGOING MAJOR ORTHOPAEDIC SURGERY.

Per P Faris, M Ritter, R Abels, D Gordon, r-HuEPO Surgery Study Group.

From the Center for Hip & Knee Surgery, Mooresville, Indiana, USA.

Background & goal of study: This study was undertaken to evaluate the effect of pre- and postoperative recombinant-human erythropoietin (r-HuEPO) on the amount of homologous blood exposure in the perioperative period, the hematologic effects of r-HuEPO on subjects in the perioperative period, and the general well-being of subjects before and after major orthopaedic procedures.

Materials & methods: 200 subjects were enrolled in a multicenter, randomized, double-blind, placebo-controlled study and divided into 3 groups: r-HuEPO 300 and 100 U/kg/day and placebo. A total of 15 doses were given s.q. beginning 10 days pre-op and extending to the 4th postop. day. Subjects were informed of the investigative nature of the study, maintained on oral iron supplements, and did not preoperatively donate autologous blood. Laboratory analysis included hemoglobin, hematocrit, reticulocyte counts and EPO antibody testing. Reports of adverse events, incidence of homologous transfusions, and energy assessments performed on an analog scale were also recorded. Decision to transfuse was physician dependent.

Results & discussion: 185 of the 200 originally enrolled subjects received ≥ 14 doses, making them evaluable for efficacy. Discontinuations were predominantly due to adverse events, none of which resulted in sequelae. There was not statistically significant differences between the groups in subject completion, sex, age, ethnic origin, surgical procedure, diagnosis, any preoperative laboratory data, or number of subjects excluded from efficacy evaluation. Prestudy to presurgery changes in hematocrit were from 38.8 to 41.2% (r-HuEPO 300, $p<0.002$)) from 39.6 to 41.4% (f-HuEPO 100, $p<0.002$), and from 38.9 to 37.3% (placebo, n.s., $p=0.001$ comp. to r-HuEPO groups). In addition, during this period, reticulocyte counts changed from 1.6 to 5.4% (r-HuEPO 300, $p=0.001$), from 1.5 to 4.6% (r-HuEPO 100, $p=0.001$), and from 1.6 to 1.7% (placebo, n.s., $p=0.001$ comp. to r-HuEPO groups). Homologous transfusion was required by 16.7% (r-HuEPO 300), 25.0% (r-HuEPO 100), and 53.7% (placebo, $p<0.001$ comp. to r-HuEPO groups) of subjects. No differences in energy assessments were identified between groups and there was no new development of anti-EPO antibodies during the study.

Conclusions: r-HuEPO successfully reduced the need for homologous transfusions in the perioperative period in subjects undergoing major orthopaedic surgery. None of the adverse experiences were significantly more prevalent among r-HuEPO-treated than among placebo-treated subjects and reported events exhibited no clinical significance in this study. Presurgery hemtocrits and reticulocyte counts significantly increased, with a resultant perioperative decrease in the need for homologous transfusions in the r-HuEPO groups compared to placebo.

A.102

PEROPERATIVE AUTOTRANSFUSION IN EMERGENCY SURGERY FOR SPINE TRAUMA.

Bruno Riou, Silvana Cavallieri,
Raymond Roy-Camille, Pierre Viars.
Departments of Anesthesiology, and Orthopedic and
Trauma Surgery, CHU Pitié-Salpêtrière, Paris,
France.

Background and goal of the study: Emergency surgery for spine trauma induces significant blood loss, requiring blood transfusion. Peroperative blood salvage is often the only technique which could be applied during emergency surgery for spine trauma, but it has never been assessed during this condition. Thus, we assessed the efficacy of peroperative autotransfusion during emergency surgery for spine trauma.

Patients and methods: We retrospectively analyzed 230 consecutives cases of emergency surgery for spine trauma (1989-92) admitted to a single level 1 Trauma Center. Patients who required perioperative (<24 hrs) blood transfusion were included and divided into 2 groups : those who benefited from intraoperative autotransfusion (Cell-Saver^R, Haemonetics) and those who did not (Control). Anesthesia was usually induced with thiopental and maintained with nitrous oxide, isoflurane, and fentanyl, and muscle relaxation achieved with vecuronium, . Surgery was performed in the prone position and included reduction, laminectomy, and fixation using plates and pedicle screws. Data are mean ± SD.

Results: Among the 230 patients, 109 required blood transfusion : 65 were control and 44 were in the Cell-Saver group. There were no significant differences between the 2 groups for sex ratio, incidence of spinal cord injury (62 %), incidence of dorsolumbar (72 %) versus cervical injury, and Injury Severity Score (24 ± 12), but significant differences in age (40 ± 18 vs 32 ± 13), duration of surgery (211 ± 93 vs 267 ± 87 min), crystalloïd (2223 ± 968 vs 2669 ± 1186 ml) and colloid (1669 ± 1238 vs 2159 ± 1238 ml) administration were noted between Control and Cell-Saver Groups, respectively. In the Cell-Saver Group, homologous blood transfusion was significantly reduced (538 ± 952 vs 1173 ± 1183 ml, $p<0.005$) as well as the number of patients who received homologous blood (45 vs 81 %, $p<0{,}001$).

Conclusion: Peroperative autotranfusion using the Cell-Saver technique enabled a significant reduction in homologous blood transfusion in emergency surgery for spine trauma.

A.103

EFFECTS OF POSTOPERATIVE AUTO-TRANSFUSION IN SPINE SURGERY

Bruno Riou, Marco Guerrero, Michel Arock, Mauricio Ramos, Pierre Viars

Departments of Anesthesiology and of Emergency Biology, Groupe Hospitalier Pitié-Salpétrière, Université Paris VI, Paris, France

Background and goal of the study: In orthopedic surgery, postoperative bleeding may be important. Although the efficacy of postoperative autotransfusion of shed blood in orthopedic surgery has been recently demonstrated, there is still limited data on its biological effects. The goal of our study was to assess these effects after spine surgery.

Patients and methods: After ethical approval and written informed consent had been obtained, 50 patients undergoing spinal surgery were randomly allocated to Control (n=25) and Solco (n=25) groups. Both groups had their postoperatively (5 hrs) drained blood collected (Solcotrans Orthopedic Plus^{R}) but only the Solco group underwent reinfusion if volume was > 200 ml. Venous blood was withdrawn preoperatively, and 5, 8 and 24 hours postoperatively, and 15 min following reinfusion. Drainage blood was also withdrawn. The following parameters were measured : hematocrit (Ht), platelet count (P), partial activated thromboplastin time (APTT), prothrombin time (PT), fibrinogen (F), and plasma potassium (K^+), free plasma hemoglobin (fHb) and D-dimers concentrations. Aerobic and anaerobic blood cultures were performed. Data are mean ± SD.

Results: The shed blood had elevated level of D-dimers, did not clot, was sterile and showed : Ht : 0.26± 0.11 ; P : 80 ± 63 $G.l^{-1}$; F < 0.1 $g.l^{-1}$. The volume collected was > 200 ml in 21 patients in the Solco group who were autotransfused (382 ± 101 ml, range 200-600 ml), and in 16 patients in the Control group. Within 15 min following reinfusion there was a moderate decrease in P (181 ± 74 vs 224 ± 90 $G.l^{-1}$, $p<0.001$), and F (2.1 ± 0.8 vs 2.3 ± 0.9 $g.l^{-1}$, $p<0.02$), and an increase in circulating D-dimers ($p<0.001$) without modifications of PT, APTT, Ht, fHb and K^+. Blood cultures were sterile. No side-effects were observed. There were no significant differences in any biological parameters between the two groups at the 8th (and 24 th postoperative hours.

Conclusion: Postoperative autotransfusion is a simple technique with few side-effects. It can be safely associated with other methods used to decrease homologous blood transfusion requirements.

A.104

ACUTE PREOPERATIVE PLASMAPHERESIS DURING CARDIAC SURGERY

G Armellin, D Pittarello, D Penzo, GP Giron

Department of Anaesthesiology, Padua University, Italy

Background and goal of study: In the last few years much attention has been focused on preoperative autologous deposit of blood. In cardiac surgery, this technique is not always feasible. To reduce the use of homologous plasma and platelets in cardiac surgery we have begun a program of harvesting autologous platelet-rich plasma (PRP) from patients prior to cardiopulmonary bypass (CPB).

Materials and methods: 40 consecutive patients scheduled for major cardiac surgery were randomly assigned to two groups; (1) acute plasmapheresis (APP) harvesting autologous PRP; (2) control group. APP was started after induction of anaesthesia. Twenty percent of the estimated plasma volume was removed and replaced with colloids. APP was performed by means of the Haemonetics Plasma Collection System Untralite. This method involves removal of blood into a centrifuge to separate it into PRP and red cells. Using a single needle technique blood was collected from the internal jugular vein while an anticoagulant was immediately added. After plasma separation was completed, the red cells were retransfused through the same needle. The PRP was retransfused at the end of CPB after heparin reversal. The following parameters were measured: haemoglobin, haematocrit, number of platelets, white and red blood cells, osmolarity, amount of total proteins, fibrinogen level, prothrombin time, partial thromboplastin time and electrolytes. Blood samples were taken before operation, at the arrival in the ICU, and 24 and 48 h later. Blood loss from the chest tube drainages and use of homologous blood products were recorded.

Results and discussion: The two groups were comparable with regard to demographic data, type of operation, duration of anaesthesia, CPB and ischaemia time. There were no differences between measured laboratory parameters in the two groups. In contrast average plasma usage and albumin usage were lower in the APP group (0.94 vs 2.39 units, $p<0.05$ and 2.18 vs 4.40 units, $p<0.05$ respectively). Our study was initiated to determine the effects of autologous PRP collected immediately before CPB upon homologous plasma and platelet usage. It demonstrates that APP resulted in significant savings of albumin and plasma.

Conclusion: We can affirm that APP is easy to perform, safe and economic. It might be another step to minimize patients' exposure to homologous blood products. APP can be performed even in patients with low haemoglobin in whom acute normovolaemic haemodilution is contraindicated. Further studies with larger patient materials are needed to finally establish the role of this technique in cardiac surgery.

Reference: Boldt J, et al: Preoperative plasmapheresis in patients undergoing cardiac surgery procedures. Anesthesiology 1990; 72:282-288.

A.105

TRANSCRANIAL DOPPLER SONOGRAPHY: EFFECT OF PROPOFOL AND THIOPENTAL IN PATIENTS WITH BRAIN TUMORS AND BRAIN INJURIES

Werner Schregel, Christoph Geißler, Udo Bredenkötter, Heinrich Schäfermeyer

Department of Anaesthesia and Intensive Care Medicine, Ruhr-Universität Bochum (RUB), Bochum, FRG

Background and goal of study: Transcranial Doppler sonography (TCD) permits noninvasive measurement of the flow velocities (v) in the middle cerebral artery (MCA). Assuming unaltered cross-sectional vessel area (VA) of the MCA, alterations of v indicate altered cerebral blood flow (CBF). The effect of anaesthetic agents on the human MCA has not been clearly determined due to ethical and methodological problems. Aaslid has pointed out, that backscattered Doppler-power is proportional to transcranial "VA" (1) of the MCA.
Material and methods: After approval of the ethical committee (RUB) six groups of 12-15 patients with brain tumors, brain injuries or without cerebral lesions were investigated if Propofol (P) or Thiopental (T) were indicated for anaesthesia or sedation. The TCD-probe was directed to the MCA (45 mm). v and "VA" were analyzed with the TCD-device 2000 S (EME) before and after 1-2,5 mg/kg P or 2-5 mg/kg T.
Results and discussion: P or T did not influence "VA". The observed reductions of v are likely to reflect real CBF-reductions induced by T or P. v decreased by 44 % (P) respectively 27 % when T was administered in patients without cerebral lesions; the reactivity to P or T was reduced or absent in some patients with brain injuries or brain tumors. Similar results (^{133}Xe) predicting an unfavourable outcome were reported by Cold (2).
Conclusion: P and T exert their vasoconstrictive effects on cerebral arterioles. TCD seems useful to monitor CBF-reductions induced by P or T. TCD-determined P- or T-reactivity may thus become a prognostic method in neurosurgical patients.

References: 1. Aaslid, R: Cerebral autoregulation dynamics in humans. Stroke 1989; 20:45-52.
2. Cold, GE: Measurement of CO_2-reactivity and barbiturate-reactivity in patients with severe head injury. Acta Neurochir 1989; 98: 153-163.

A.106

JUGULAR BULB METABOLIC MONITORING DURING HYPERVENTILATION IN SEVERE HEAD TRAUMA PATIENTS

Cathy De Deyne, Tom Vandekerckhove, Johan Decruyedaere, Jan Poelaert, Francis Colardyn

Department of Intensive Care, Universital Hospital, Ghent, Belgium

Background and goal of study: In the present study, we analyzed the possibly ischaemic events during hyperventilation of patients with severe head trauma by monitoring jugular bulb metabolic data.

Materials and methods: Twenty patients suffering from severe head injury (GCS<8) were selected. They all had intracranial hypertension with an ICP above 20 mm Hg as measued by an intraventricular catheter despite optimal management incuding sedation, normoventilation, CSF drainage and iv mannitol. The patients were hyperventilated over 6 h, decreasing paCO2 from a mean of 34 mm Hg to a mean of 25 mm Hg. During this period, we continuously monitored jugular bulb oxygen saturation (SjO2) by the oximetry technique. In addition, we sampled blood for determination of the jugulo-arterial lactate concentration difference (jADL) before and at the end of the 6 h period.

Results and discussion: Eleven patients showed a significant decrease (e.g. > 5% units) of SjO2 during hyperventilation, eight of whom also had a significant increase of jADL (e.g. > 1.0 mg/dl). Six of these eleven patients had a lactate/oxygen index (jADL/AVjDO2 > 0.4 mg/dl/Vol%), strongly suggesting the development of brain oedema during hyperventilation. Despite 12/20 patients demonstrating decreasing ICP after institution of hyperventilation, six of the 12 had jugular bulb metabolic indices of brain ischaemia with this therapy.

Conclusions: These results again confirm the idea that "blind" hyperventilation could do more harm than good. However, hyperventilation remains an effective therapy against intracranial hypertension, provided jugular bulb metabolic data are used to guide safe hyperventilation.

A.107

SUFENTANIL INCREASES INTRACRANIAL PRESSURE IN PATIENTS WITH HEAD TRAUMA

Jacques Albanese, Xavier Viviand, Olivier Durbec,
Bernard Alliez, Claude Martin

DAR Hôpital Nord - 13326 Marseille - Cedex 15
France

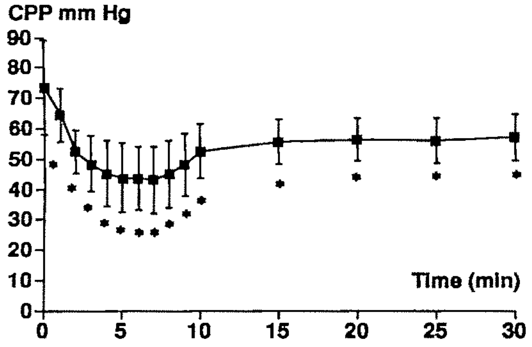
Background and goal of study : several recent studies in both animals and humans have suggested that sufentanil may be associated with significant increases in cerebral blood flow (CBF) and/or intracranial pressure (ICP) (1,2). The safety of using these agents in neurosurgical patients is thus controversial.

Materials and methods : the subjects were 10 mechanically ventilated head injured patients (with informed consent from family and approval by the Research Commitee of our institution). After obtaining control of ICP (between 15 and 25 mmHg) hemodynamic values and blood gas tension (PaCO2 between 30 and 35 mmHg) with propofol infusion and mechanical ventilation, the level of sedation was deepened with an IV bolus injection of sufentanil (1mg/kg/6min) followed by an infusion of 0.005 mg/kg/min. Mean arterial pressure (MAP), ICP (fiberoptic intracranial pressure monitor) and end-tidal CO2 were continuously measured and recorded at 1 minute intervals throughout the 30 minute study period. The cerebral perfusion pressure (CPP) was calculated by subtracting ICP from MAP.

Results and discussion : sufentanil produced a significant increase in ICP (70% increase) which peaked at 5 min, then gradually decreased and return to baseline after 15 min (Fig1). This was accompanied by a significant decrease in MAP (19.5% decrease) and thus in CPP (37% decrease) (figure). After 5 min, MAP and CPP gradually increased but remained signicantly decreased throughout the study.

Conclusion : this study shows that in the presence of decreased intracranial compliance, the increase in CBF produced by bolus injection of sufentanil was accompanied by an important increase in ICP which can result in a risk of cerebral ischemia, since CPP decreased dramaticaly below 45 mm Hg. During sufentanil infusion which followed the bollus, ICP returned to baseline, and CPP remained greater than 55 mm Hg.

References : 1Anesthesiology 69: A627, 1988. 2 Anesth Analg 68: S196,1989



Mean ± SD CPP over time after IV bolus of sufentanil. Values were plotted at 1 min intervals after drug administration during the first 10 min. * $p < 0.05$ compared to baseline value using Dunnett's test

---

A.108

CARDIAC FUNCTION IN ANEURYSMAL SUBARACHNOID HAEMORRHAGE

Nadia Moulay, Véronique Mahé, Adrien Descorps-Déclère,
Claudine Cosson, Claude Ecoffey.

Département d'Anesthésie - Réanimation, Université Paris-Sud, Hôpital de Bicêtre, 94275 - Le Kremlin-Bicêtre,
FRANCE

Background and goal of study: Electrocardiographic (ECG) changes occur frequently after subarachnoid haemorrhage (SAH) (1). The aim of this study was to investigate the significance of ECG changes by echocardiographic assessment of cardiac function and by serum creatine kinase dosage.

Material and methods: Between May 92 and October 92, we studied prospectively, all the patients with SAH documented by computed tomography scanning and cerebral angiography and admitted to the hospital the first day after the bleeding. We recorded age and neurological status (Hunt and Hess' score). ECG were performed twice daily for the first 3 days after the admission, they were considered abnormal if the T wave was inverted or flattened, the S-T segment was elevated or depressed or a pathological Q wave was present. echocardiography (echo) was performed initially before the third day and after 10 days if the first exam showed abnormalities: hypo-, a- or dyskinesia. Creatine kinase, i.e. total and isoenzyme MB (CK-MB) was dosed by immunoenzymometric assay and a calculated ratio > 1.5 was considered pathological.

Results and discussion: The individual values were summarized in the table:

patients	age yrs	G	T	S-T	Q	CK-MB	echo < day 3	E
1	42	1		X			N	
2	28	2				-	N	
3	69	2	X	X		-	N	
4	45	2	X	X		X	A N	S
5	54	2				-	N	
6	41	2	X			-	N	S
7	33	4	X	X		X	N	S
8	72	2	X			-	N	
9	66	3		X	X	X	N	S
10	40	3	X		X	X	N	
11	24	2					N	
12	68	4			X		N	D
13	38	4	X				A N	D
14	39	1				-	N	
15	25	1	X			-	A N	
16	29	2				-	N	
17	60	3				-	N	
18	69	3		X		X	A N	D
19	46	2				-	N	
20	48	4				-	N	

G: Hunt and Hess grade; T: abnormality of the T wave, S-T: change of the S-T segment, Q: pathological Q wave presence; E: evolution, S: intracranial arterial spasm; D: death.

As previously reported, we found a relationship between the increase in the CK-MB and the incidence of ECG changes (2) and the severity of neurologic state (3). Nonetheless, there was no close relationship with the abnormalities of the myocardial wall motion; these changes were transient (patients 4 and 15 had an echo normal at day 10, patients 13 and 18 were died within 10 days). In addition, patient 4 had a clinical pulmonary oedema which was resolved rapidly with diuretic therapy.

Conclusion: In spite of the absence of a close relationship between the ECG changes and the abnormalities of Echo we recommend to perform an echocardiographic assessment of cardiac function in aneurysmal subarachnoid haemorrhage.

References: 1) Harries AD: Postgraduate Med J 1981; 57: 294-296, 2) Pollck C et al: J Am Coll Cardiol 1988; 12: 600-605, 3) Fabinyi G et al: J Neurol Neurosurg Psych 1977; 40: 818-820

A.109

EXTERNAL VENTRICULAR CSF DRAINS INFECTIONS

Véronique Mahé, Nathalie Kermarrec, Claude Ecoffey

Département d'Anesthésie - Réanimation, Université Paris-Sud, Hôpital de Bicêtre, 94275 - Le Kremlin-Bicêtre, FRANCE

Background and goal of the study : The main complication of external ventricular CSF drains (EVD) was infections. We performed a retrospective study to assess the relationships among EVD duration, systemically administered antibiotics and CSF infections.

Material and methods : 63 EVD inserted from January 90 to December 91 in 54 neurosurgical patients ,whose age ranged from 7 to 76 years and IGS from 1 to 20, were analyzed in this study. CSF withdrawn from the drain was collected daily for laboratory bacteriological, biochemical and cytological analysis and microbiological culture, until the EVD removal. The daily glycemia and administered antibiotics (AB), the EVD duration, the day a colonization and/or an infection occurred were recorded. A CSF colonization was defined by a positive direct examination or a positive culture of CSF without biochemical and cytological abnormalities. The diagnosis of CSF drain infection was established by a low glucose value or leucocytosis without a blood contamination, however the bacteriological analysis results were affected by the previous antibiotic treatment.

Results and discussion : Underlying neurosurgical pathologies, age, IGS, CGS and the delay between the hospital admission and the day of drain insertion were the same in both groups. The other results (mean ± SD) were as follows:

EVD	n	D (day)	d (day)	AB (appropriate)
without infection	25	8 ± 4		16
colonization	27	16 ± 12*	5±4	16(10)
infection &	22&	18 ± 13*	10±9	15(10)

& 12 EVD with colonization before infection; * p < 0,01 vs without infection, D: EVD duration, d: delay between insertion and colonization or infection, appropriate AB: isolated pathogens were susceptible to previous AB.

EVD	n	SC	SA	Others	Meningitis
colonization	27	13	5	9	
Infection	22	6	5	5	6

S C : coagulase negative staphylococci, S A : staphylococcus aureus.

For 6 patients, AB was effective to treat a meningitis: there was leucocytosis with low glucose value but microbiological culture remained negative.

Conclusion : There was a significant association between infection and colonization rates and the duration of EDV but the systemic antibiotics therapy has no effect. Probably local administration of antibiotics should be more efficient for treatment of EDV infection.

A.110

EEG-MONITORING DURING DEFIBRILLATOR-IMPLANTATION: EFFECTS OF REPETITIVE CEREBRAL ISCHEMIA ON ELECTRIC BRAIN ACTIVITY

[*]C.Spies, [$]S.Kraemer, [*]T.Heil, [*]T.Neumann, [*]K.Reinhart

[*]Department of Anaesthesia and Intensive Care Medicine,
[$]Department of Neurology, Steglitz Medical Center,
Free University Berlin, Berlin, Germany

Background and goal of study: Implantation of an internal automatic cardioverter defibrillator (ICD) is a therapeutic regimen for malignant tachyarrhythmias.[1] To assess the individual defibrillation threshold repetitive induction of ventricular fibrillation is required. During each testing cardiac arrest and, hence, intermittent interruption of cerebral perfusion occurs, which can be registered by EEG-monitoring of electric brain activity.[2] There are hints that repetitive interruption of cerebral perfusion is associated with a decreased ischemic tolerance.[3] We investigated whether time course and number of intraoperative testing influenced duration and reversibility of EEG changes.

Material and methods: In 15 male patients, aged 59 +/- 5 years, extended perioperative monitoring (pulmonary and radial artery catheter, pulse oximetry, capnography, temporary pacemaker) and balanced anesthesia were performed. Conventional six channel EEG (lead position at the International 10-20-System: FP1-C3, FP2-C4, C3-O1, C4-O2, F7-T5, F8-T6) was continuously recorded. The curves were evaluated visually. Statistical analysis was performed by the Wilcoxon rank-sum test.

Results and discussion: Duration of EEG changes significantly increased with the number of testings (p=0.001, fig.1) and with the duration of cardiac arrests (p=0.037). Shorter intervals between testings also significantly increased the duration of EEG changes (p=0.001). EEG changes outlasting operation were found after the fourth testing in individual patients and were observed more frequent with increased numbers of testings (p=0.003).

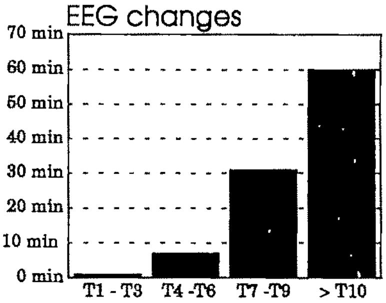


Fig.1: Number of testings

Conclusion: Intraoperative EEG-monitoring can detect cerebral hypoperfusion. Before induction of further testings restitution of electric brain activity can be evaluated by intraoperative EEG-monitoring.

Reference: 1. Pace 1991;14:297-301, 2. Anesthesiology 1990; 73:821-825, 3. Pace 1991; 99:1899-1904.

A.111

MIDAZOLAM PREVENTS KETAMINE-INDUCED STIMULATION OF CEREBRAL METABOLISM

Jonas Åkeson, Sven Björkman, Kenneth Messeter

Departments of Anaesthesia and Intensive Care, and
Experimental Research, Lund University,
Malmö General Hospital, and Hospital Pharmacy,
Malmö General Hospital, Malmö, Sweden

Background and goal of study: An anaesthetic dose of ketamine induces a biphasic metabolic response of the brain including a delayed increase in the cerebral metabolic rate for oxygen ($CMRO_2$) and a sustained decrease in cerebral blood flow (CBF) *[1]*. Midazolam has been reported to attenuate clinical symptoms of excitation during ketamine anaesthesia. We have thus studied the cerebral haemodynamic and metabolic responses to ketamine in combinations with low doses of midazolam.

Materials and methods: Cerebral variables were assessed on five occasions during an 80 min period following rapid infusion of ketamine (10.0 $mg \cdot kg^{-1}$) and midazolam (0.10 or 0.25 $mg \cdot kg^{-1}$) in twelve normoventilated pigs anaesthetized with fentanyl, nitrous oxide and pancuronium *[2]*. CBF was calculated from the initial slope of the cerebral clearance curve of ^{133}Xe injected into the internal carotid artery and recorded by an extracranial scintillation detector.

Results and discussion: Both drug combinations augmented the haemodynamic depression and prevented metabolic stimulation of the brain as compared with ketamine alone. A 45% decrease in CBF ($P<0.001$) induced by the 0.25/10 midazolam/ketamine regimen was found to be associated with a 40% increase in CVR ($P<0.05$). Systemic blood pressure was similarly influenced by ketamine-midazolam and ketamine.

Conclusions: A ketamine-midazolam combination comprising 1-2.5% midazolam is superior to ketamine alone for anaesthetic use. Compensatory pharmacodynamic effects on $CMRO_2$ are probably involved in the attenuation by midazolam of excitatory cerebral symptoms associated with ketamine anaesthesia.

References: 1. Åkeson J, Björkman S, Messeter K, Rosén I, Helfer M. Acta Anaesthesiologica Scandinavica 1993;37 (in press). 2. Åkeson J, Nilsson F, Ryding E, Messeter K. Acta Anaesthesiologica Scandinavica 1992;36:419-426.

A.112

NITROUS OXIDE INDUCED NEURONAL DEPRESSION: MODIFICATION THROUGH BENZODIAZEPINE RECEPTORS

M. Dzoljic, E. Geller, J. Rupreht, W. Erdmann
M.R. Dzoljic
Department of Anaesthesiology, Faculty of Medicine
Erasmus University, Rotterdam, The Netherlands

Background and goal of study: The high correlation between the lipophilicity and the potency of anaesthetic agents has been interpreted as evidence that general anaesthesia occurs secondary to a non-specific disruption of neuronal cell membranes lipids. The extent to which the above hypothesis is accurate is questionable and the mechanism(s) through which such drugs produce unconsciousness, amnesia and analgesia remains unclear. Recent studies suggest more specific interaction through membrane proteins. The purpose of this study was to determine the extent of nitrous oxide (N_2O)-induced neuronal depression, by measuring the visual evoked potentials (VEP) after exposure to Ro 15-4513. This partial inverse agonist was chosen because of its specific interaction with ethanol induced depression, which is able to accomplish cross-tolerance with N_2O (1).

Materials and methods: VEP were recorded in 20 free moving Wistar rats before and during exposure to 70 % N_2O in oxygen (O_2). After 1 hr of exposure to N_2O, Ro 15-4513 (10 mg/kg) or the solvent Tween (0.3%), i.p. was given. An other group of 10 rats were given Ro 15-4513, (10 mg/kg) i.p. while breathing air to ensure the drug doesn't have an epileptogenic property given at this concentration. With 15 min intervals three VEP recordings were made and the peak latencies as well as the peak-to-peak amplitudes were determined.

Results and discussion: While breathing 70 % N_2O in O_2 there were no significant changes in latencies of the first 6 peaks, although the longer latencies showed a tendency towards an increase. All first 5 peak-to-peak amplitudes showed a significant depression during exposure to N_2O, which was partially but significantly reversed by Ro15-4513 but not by the solvent Tween. Ro15-4513 given to rats while breathing air did not increase the amplitudes suggesting its effects were not aspecific but related to a change induced by N_2O.

Conclusion: We conclude that depression as induced by N_2O can partially be reversed by Ro15-4513, a benzodiazepine inverse agonist. This partial reversal of N_2O anaesthesia indicates that central depression might be due to an interaction between N_2O and a binding site of GABA-A complex directly or through pertuberation of the membrane surrounding the macromolecule.

Reference: 1) Koblin, D.D, et al: Mice tolerant to nitrous oxide are also tolerant to alcohol. J. Pharmacol. Exp. Ther.1980:213:309-312..

A.113

Dexmedetomidine does not exercise its anesthetic action through GABA.

Markku Salonen, Joan Kendig, Billy O'Connor, Mervyn Maze.
Department of Anesthesia, Stanford University, Stanford CA & Turku University, Turku, Finland

In our earlier studies, we have demonstrated a significant sedative synergistic interaction between midazolam and dexmedetomidine in rats (Salonen et al 1991). Midazolam, similarly to many other anesthetic agents, is considered to cause its main action through potentiating GABA's actions. In this series of studies we wanted to seek the possible involvement of GABA-ergic components in the synergy found between dexmedetomidine and midazolam.

The following possibilities were examined:

1) **Presynaptic**: Dexmedetomidines effects on *GABA-release* in the neonatal rat spinal cord model. 20 nM Dexmedetomidine was applied onto spinal cords bathing in the artificial CFS. 100 nM rauwolscine was used as an antagonist, and high potassium as a positive control. The GABA concentrations were determined by HPLC.

2) **Post synaptic**: Effect of bicuculline on the inhibiting effect of dexmedetomidine on the neonatal rat *ventral root potential.* Dexmedetomidine's effect on the neonatal rat spinal cord *dorsal root potential*, which is a GABA$_A$-receptor mediated electro-physiologic response.

3) **Post synaptic**: Dexmedetomidine's effects on the GABA-stimulated *chloride-flux* in rat cortical synaptosomes. Chloride flux was assayed in the presence and absence of midazolam. The effect of GABA induced desensitization on the chloride flux was also measured.

RESULTS: Bicuculline was capable of blocking dexmedetomidine's inhibiting effect on the ventral root potential. The dorsal root potential was not affected by dexmedetomidine. No effect was seen in GABA-release or GABA-stimulated chloride flux.

CONCLUSION: Dexmedetomidine seems to represent a particular category within anesthetic agents, not involving GABA-ergic transmission. We conclude that GABA is not involved in the synergistic interaction between alpha$_2$ agonists and benzodiazepines.

REFERENCES: Salonen M et al: Synergistic sedative interaction between alpha$_2$ agonists and benzodiazepines in rats. Anesthesiology 1992 Jun;76(6):1004-11 .

A.114

DIFFERENTIAL EFFECTS OF SPECIFIC DELTA AND KAPPA OPIOID ANTAGONISTS ON THE BIDIRECTIONNAL EFFECT OF NALOXONE IN ARTHRITIC RATS.

I.Cattaneo, V.Kayser, G.Guilbaud

Unité de Recherches de Physiopharmacologie du Système Nerveux, INSERM U 161, Paris, France

Background and goal of the study: Previous behavioural studies have shown that naloxone (Nx) induces bidirectionnal effects in arthritic rats (1). The goal of this study was to determine the opioid receptor classes underlying these two effects, using δ and κ antagonists.
Materials and methods: We used 220 male Sprague-Dawley rats rendered arthritic by the inoculation of Freund's adjuvant. As a nociceptive test we used the measure of the vocalization thresholds to paw pressure. Firstly we determined the doses of the δ-antagonists (ICI-174,864 and naltrindole) and of the κ–antagonist (MR2266) without analgesic or hyperalgesic action per se (respectively 10mg/kg, 1mg/kg and 0.2mg/kg iv). Secondly, we confirmed the specificity of each antagonist, on the antinociceptive effect of specific agonists (δ-agonist DTLET, κ–agonist U69593, μ-agonist DAMGO and morphine). Thirdly, we observed the action of these two antagonists on the paradoxical analgesia produced by 3μg/kg iv of Nx and on the hyperalgesia produced by 1mg/kg iv of Nx.
Results and discussion: The hyperalgesic effect of high doses of Nx was significantly reduced by 50% after the injection of the δ-antagonists. This suggests the involvement of δ-opioid receptors in a tonic inhibitory control exerted on nociceptive messages by endogenous opioid. The paradoxical effect of low doses was almost abolished by the κ–antagonist (85% decrease of the analgesic effect). This involvement of the κ–receptors supports as previous biochemical studies (2) the hypothesis of presynaptic κ–receptors which may modulate the release of endogenous opioid.
Conclusion: In this model of persistent pain, the bidirectionnal effect of Nx involves the δ-receptors for the hyperalgesia and the κ–receptors for the paradoxical analgesia.

References: (1) Kayser V et al.: Dose-dependent analgesic and hyperalgesic effects of systemic naloxone in arthritic rats. Brain Res., 1981; 267:131-138.
(2) Ueda H. et al.: Presynaptic opioid k-receptor and regulation of the release of Met-enkephalin in the rat brainstem. Neurosciences Letters, 1987, 81:309-313.

A.115

EFFECT OF MORPHINE ON A NOCICEPTIVE FLEXION REFLEX IN PATIENTS WITH POSTOPERATIVE PAIN

Marcel Chauvin - Frédéric Guirimand, Pascal Gauneau, Claude Lebrault
Department of Anesthesiology, Hôpital Ambroise Paré,
92104 BOULOGNE Cedex, France

Background and goal of study: Intravenous (IV) morphine was shown to depress selectively the lower limb nociceptive flexion (RIII) reflex in volunteers (1) and in chronic paraplegic subjects (2), suggesting that IV morphine exerts a direct spinal inhibition of nociception. However, the time course of this spinal antinociceptive action was not evaluated in comparison with the duration of analgesia, and the extrapolation of these data to painful patients remains questionable . The present work was undertaken to assess the spinal effect of an IV dose of morphine in patients with postoperative pain.

Materials and methods: 20 adult ASA I or II patients, studied during the postoperative period were randomly assigned in a double blinded fashion either to group M (n = 10) which received IV morphine (0.16 mg/kg), or group P (n = 10) which received IV placebo (5 ml of isotonic saline solution) when they complained of severe pain. The intensity of postoperative pain was assessed on a visual analog scale (VAS). RIII reflex was studied according to a method previously described (1). The recruitment curves were recorded before, and at intervals after IV injection. A constant intensity of 1.2-1.3 times threshold (Tr) was applied between the recruitment periods. Data are reported as mean ± SD. Statistical analysis used paired or unpaired Student's t-test as required.

Results and discussion: Results are summarized in the table. Tr increased and the slope of the recruitment curve decreased in all group M patients. These changes were significant at 15 and 30 min. The decrease in RIII reflex under constant stimulus intensity appeared at 2 min and was significant during 30 min; the maximum decrease, seen at 5 ± 1 min, was of 86 ± 7%. By contrast, pain relief lasted 4 hours. Placebo study was stopped after 15 min because analgesics were required. This study demonstrates that in patients with postoperative pain, IV morphine produces a depression in RIII reflex at the dose of 0.16 mg/kg. These data support the hypothesis that, at this dose, IV morphine has a direct effect within the spinal cord. However, this spinal effect had a more limited duration than the pain relief, suggesting that the supraspinal action of IV morphine lasts longer than the inhibitory action at the spinal site.

Références : 1- Willer JC. Brain Res 1985; 331: 105-114. 2- Willer JC, Bussel B. Brain Res 1980; 187: 212-215.

TIME (min)		Control	15	30	60	120
VAS	GM	7.6±1.6	1.5±2.0*	0.7±1.0*	0.9±0.8*	1 2±1.5*
Score	GP	7.5±1.5	7.7±1.7†			
Tr	GM	8.7±3.0	11.9±3.5*	11.5±3.1*	9.6±1.9	8.1±2.8
(mA)	GP	8.8±1.7	8.4±1.2†			
% change	GM		-25±21*	-29±20*	-27±47	-3±91
in slope	GP		3±4†			

*p < 0.05 vs control - †p <0.05 vs GM Mean ± SD

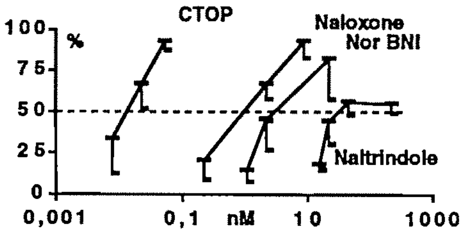
A.116

INVOLVEMENT OF μ, δ, and κ RECEPTORS IN THE INHIBITION BY INTRATHECAL MORPHINE OF A C-FIBRE EVOKED REFLEX IN THE RAT.

F. GUIRIMAND*, M. STRIMBU, J.C. WILLER**, D. LE BARS, INSERM, U-161, 75014 Paris, *Dép. Anesthésie; Hôp. A. Paré, 92100 Boulogne, ** lab. Neurophysiologie, Hôp. Pitié-Salpétrière, 75013 Paris.

By means of specific μ (CTOP), δ (naltrindole) and κ (nor-BNI) antagonists injected intrathecally, we studied the involvement of the opioid receptors in analgesia due to morphine at the spinal level. The nociceptive response was a C-fibre evoked reflex elicited by single-square electrical shocks (2 ms, 0.16 Hz) applied to the territory of the sural nerve of intact halothane anesthetized (0.9 %) rats. EMG-evoked responses, recorded by means of a pair of Pt-Ir electrodes inserted transcutaneously in the ipsilateral biceps femoris, were digitized, fullwaved rectified and C-fibre responses (at 3x threshold) were integrated in an adequate window (100 - 450 ms). Morphine was injected intrathecally in a dose (2.2 nM) that completely inhibited the reflex. Naloxone (0.22 - 8.8 nM) reversed the effect of morphine dose-dependently, with an ED_{50} = 1nM. The corresponding dose-response curve for naltrindole (15.4 - 220 nM) was shifted to the right (ED_{50} = 34.4 nM) with a maximal effect of 56 %. As expected, the dose-response curve corresponding to CTOP (0.0055 - 0.055 nM) was shifted to the left (ED_{50} = 0.01 nM). More surprinsingly, the specific κ antagonist nor-BNI (1.1 nm - 22 nM) also fullly reversed the effect of morphine dose-dependently (ED_{50} = 4.32 nM). The results confirm the importance of μ receptors in morphine-induced analgesia. The involvement of δ and κ receptors is possible, although an effect of nor-BNI on μ receptors cannot be excluded.

Our conclusion is that the C-fibre evoked reflex is a model with high applicability in evaluating the effect of putative analgesic drugs.



A.117

ISOPROTERENOL REVERSES THE MAC DECREASING EFFECT OF ESMOLOL IN RATS.

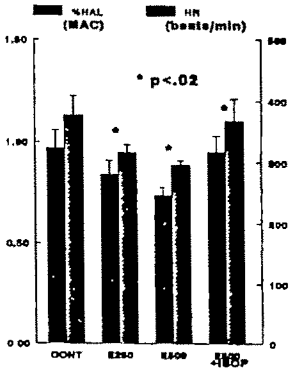
Azriel Perel, Alexander Shneider, Walter Kohn,
Department of Anesthesiology, Sheba Medical Center,
[Sackler School of Medicine, Tel Aviv University],
Tel Hashomer 52621, Israel.

Background and goal of study: Beta adrenergic blocking agents are known to have a depressive effect on the central nervous system. Although propranolol has not been found to reduce MAC of halothane in dogs (1), we have recently found that esmolol, a new short acting beta blocker, reduced MAC of halothane in rats (2). In addition, Kochs et al have shown that esmolol attenuates the EEG response to sensory stimulation in dogs, and that this effect was reversed by epinephrine (3). We have thus examined whether the MAC reducing efffect of esmolol is dose-dependent and whether it can be reversed by isoproterenol (ISOP).

Materials and methods: Thirty five 280-350g Sprague-Dawly male rats were included in the study and divided into 4 groups: 1. A control group (n = 10). 2. A group that received a continuous drip of 250 mcg/kg/min of esmolol (E250) (n = 8). 3. A group receiving 500 mcg/kg/min of esmolol (E500) (n = 8). 4. A group that received in addition to E500, a continuous infusion of ISOP in a dose that normalized heart rate to its pre-esmolol values. The MAC of halothane was determined by the tail clamp method in each group.

Results: Esmolol reduced the MAC of halothane in a dose dependent fashion (fig), the MAC decreasing from 0.97% during baseline (BL), to 0.84 and 0.74 during the administration of E250 and E500 respectively. The addition of ISOP (2.9±0.4 mcg/kg/min) to E500, brought MAC back to control values. The systolic blood pressure (at 0.9% halothane) was reduced from 152±16 to 122±10 and 109±10 mm Hg during E250 and E500 respectively, and returned to normal levels with isoproterenol. The changes in HR are shown in the figure. There was no change in the arterial blood gases at any point in the study.

Discussion and conclusions: The most probable explanation for the MAC reducing effect of esmolol is a decrease in the catecholamines content in the brain. Other studies which abolished central noradrenaline secretion have also produced about 35% decrease in the MAC of halothane (4). Isoproterenol is known to increase central catecholamines content and, most probably, counteracts the MAC decreasing effect of esmolol by this mechanism. The decrease of anesthetic requirements by a short acting beta blocker offers exciting possibilities in the administration of adequate nesthesia without using excessive amounts of conventional anesthetic agents.



References: 1. Tanifuji Y. et al, Anesth Analg 55:383,76
2. Perel A. et al, Anesthesiology, 77:A406,92
3. Kochs E. et al, Anesthesiology 77: A718,92
4. Roizen MF. et al, Anesthesiology 49:252,78

A.118

EFFECT OF ESMOLOL VERSUS LIDOCAINE ON INTRACRANIAL PRESSURE AND HAEMODYNAMIC RESPONSES TO LARYNGOSCOPY AND INTUBATION

Toufik SAMAHA, Patrick RAVUSSIN*, Chantal CLACQUIN, Claude ECOFFEY

Anaes Dpt, Hôpital de Bicêtre, Université Paris - Sud, 94275 - Le Kremlin Bicêtre, FRANCE, and
* Anaes Dpt, CHUV, CH - 1011 Lausanne, SWITZERLAND

Background and goal of the study : The prevention and control of acute increases in intracranial pressure (ICP) and mean arterial pressure (MAP) in response to nociceptive stimuli are among the main aims of neuroanaesthesia. Lidocaine (1) and more recently esmolol (2) have been advocated to be given prophylactically 90 to 180 sec before application of a noxious stimulus like intubation. The present study was undertaken to compare both agents in neuroanaesthesia during the induction phase with special attention focused on MAP and ICP variations during intubation.

Material and methods : 22 patients for elective cerebral tumor resection were included in this randomized, double-blinded study, after IRB approval and informed consent. Exclusion criteria were ICP > 25 mmHg, CV disease and obesity (> 25 % IBW). The patients were assigned to 2 groups: Group I n = 11 esmolol (E) 1.5 mg/kg, Group II n = 11 lidocaine (L) 1,5 mg/kg. Monitoring included MAP, ICP via a lumbar spinal catheter, CPP (= MAP - ICP), PetCO$_2$ (to 33-35 mmHg). Since no patient had an intracerebral lesion which might have been an obstacle to CSF flow, CSFP changes were taken to indicate ICP changes. General anaesthesia was induced in both groups over a period of 5.5 min: thiopentone 5 mg/kg followed by isoflurane 0.5 %, fentanyl 1 µg/kg and vecuronium 0.1 mg/kg. At T1 Group I received E and Group II received L both over 20 sec. In both groups, 130 sec after the end of E or L administration laryngoscopy was started by the same intubator. Isoflurane was titrated to maintain CPP above 60 mmHg. Ephedrine 5 mg was used each time CPP dropped below 60 mmHg. ICP, MAP,HR and CPP were recorded at baseline (T0), after thiopentone (T1), after E or L administration (T2), during intubation (maximal values) (T3) and 5 min after intubation (T4). Analysis of variance with Sheffe F-test and student's t-test were performed for statistical analysis.

Results and discussion : The demographic data and baseline ICP, MAP, HR and CPP were similar in E and L. The evolution of HR was similar in both groups. Four patients were given ephedrine in each group. All the results (mean ±SD, mmHg) are summarized in the table (* $p < 0.05$ vs T0).

		T0	T1	T2	T3	T4
MAP	E	103±14	84±10	75±11*	116±22	83±13
	L	106±16	87±11	80±11*	115±16	90±18
ICP	E	11±6	12±7	13±8	17±10*	9±3
	L	10±6	10±4	11±5	16±8	11±6
CPP	E	92±11	71±9	61±8*	99±23	71±10
	L	96±11	76±14	68±14*	98±17	81±18

In normotensive neurosurgical patients both L and E when added to a classical anaesthetic sequence decreased CPP to values close to 70 mmHg for L and 60 mmHg for E. Both agents during laryngoscopy and intubation protected the patients from increases in MAP and CPP as compared to baseline whereas only L (and not E) protected ICP to such increases.

Conclusion : Lidocaine seems to offer more stable MAP and CPP values during induction and a better protection for ICP increases during laryngoscopy and intubation than esmolol.

References : 1) Hamill JR et al. Anesthesiology 1981 ; 55 : 578-581, 2) Helfman SM et al. Anesth Analg 1991 ; 72 : 482-486

A.119

EFFECTS OF INTRATHECAL MEPERIDINE (MP) FENTANYL (FN) AND LIDOCAINE (LD) ON SOMATOSENSORY (SSEP) AND CORTICAL MOTOR (CMEP) EVOKED POTENTIALS IN HUMANS.

S Fernandez, J Monells*, JM Espadaler*, MM Puig

Departments of Anaesthesiology and Neurophysiology*,
Hospital del Mar, Autonomous University
of Barcelona, Spain.

The aim of the present study was to establish the effects of clinically relevant doses of LD, MP and FN on somaesthetic and motor pathways, when administered in the lumbar subarachnoid (SA) space.

Methods: Thirty ASA I-II patients (45-65 y.o.) scheduled for infraumbilical surgery entered the study. Institutional and individual consents were obtained. Drugs were administered SA (2 ml, in D7.5W) at L3-4 with a 25G needle. Patients were randomly distributed into three groups which received: LD (1 mg/kg), MP (1 mg/kg) or FN (25 ug). SSEP were obtained by stimulating the posterior tibial nerve and registered at Fz-Cz. CMEP's were elicited by magnetic stimulation at the vertex and muscle responses, at rest and facilitated, recorded from the gastrocnemius. The conduction of the motor radicular segment was assessed by the F waves. All four evoked responses (ER) were elicited from each patient in baseline conditions and 30 min after treatment; we evaluated the number and characteristics (amplitude, latency) of the ER.

Results: In baseline conditions, forty ER could be elicited from each group (n=10). After treatment, ER's were either blocked (type A), altered (type B, decreased amplitude and/or increased latency) or unchanged (C). The Table shows frequency distribution and type of response in each group.

	A	B	C
LD	40	0	0
MP	19	19	2
FE	0	27	13

By chi-square, each group was different from the others ($p<0.01$).

Our results also show that MP predominantly blocked motor responses at rest (CMEP-R) while FE altered both sensory and motor ER. The study demonstrates that clinically relevant doses of SA opiates alter motor and sensory transmission in the spinal cord.

SSEP were obtained by stimulating the posterior tibial nerve and registered at Fz-Cz. CMEP's were elicited by magnetic stimulation at the vertex and muscle responses, at rest and facilitated, recorded from the gastroecnemius. The conduction of the motor radicular segment was assessed by the F waves.

A.120

SLOW-RELEASE EFFECT OF pH-ADJUSTED BUPIVACAINE: PHARMACOKINETIC DEMONSTRATION

Dan Benhamou, Jean-Marc Malinowsky,
Valérie Quinquis, Philippe Bourget, Guy Couarraze

Département d'Anesthésie-Réanimation Chirurgicale,
Hôpital Antoine Béclère, Université Paris-Sud,
92141 Clamart, France

Background and goal of study: It has been recently demonstrated *in vitro* that pH-adjustment of local anaesthetics used during regional anesthesia is associated with a slow-release effect (1). Intramuscular injection (which usually provides pharmacokinetic data close to those obtained after epidural injection) of pH-adjusted bupivacaine (BUP) was used to determine *in vivo* the extent of changes in pharmacokinetic parameters indicative of a slow-release effect.

Materials and methods: 21 New-Zealand white non fasting rabbits (weight: 2.5-3.2 kg) were premedicated with 2-4 mg of midazolam and then immobilized. Cannulation of an ear vein (22g catheter) and of a femoral artery (20g catheter) were performed under local anesthesia with lidocaine. A radiant heat lamp was used to maintain normothermia. An intramuscular injection of 3 ml/kg of 0.5 % BUP was injected according to the randomization order : **group 1** : plain bupivacaine (pH = 5.80 ± 0.02), **group 2** : BUP alkalinized with 0.1 mEq bicarbonate/20 ml BUP (pH = 6.8 ± 0.01), **group 3** : BUP alkalinized with 0.2 mEq bicarbonate/20 ml BUP (pH = 7.2 ± 0.02). Arterial blood samples (1-1.5 ml) were withdrawn at 2, 5, 10, 15, 30, 60, 90, 120, 240 and 480 min after im injection. Plasma BUP concentrations were measured using HPLC and pharmacokinetic data were calculated using a computer-assisted program. Statistical analysis was performed using ANOVA for repeated measures.

Results and discussion: Peak plasma concentration (Cmax) was significantly decreased in group 3 (pH = 7.02) suggesting slow release and absorption from the im site of injection (table). The area under the curve (AUCo-∞) was significantly lower in both groups with pH-adjusted BUP suggesting important tissue storage (table).

Conclusion: This pharmacokinetic study confirms that pH-adjustment of bupivacaine is associated with a slow-release effect which might explain the prolonged duration of sensory block after regional anesthesia.

Reference: 1- Bonhomme L, et al: Slow-release effect of pH-adjusted bupivacaine: In vitro demonstration. Int. J. Pharmac. 1992; 84:33-37.

mean ±sem	Cmax (mg/l)	AUCo-∞ (mg/l.h)	Vd (l/kg)	$T_{1/2}$ (h)
Group 1	3.3±0.5	27±5	5.4±1.7	25.6±5.7
Group 2	2.9±0.5	14±4*	5.6±0.7	15.5±3.5
Group 3	2.4±0.3*	6±3*	18.9±9.8*	5.6±1.3*

* p<0.05 versus Group 1

A.121

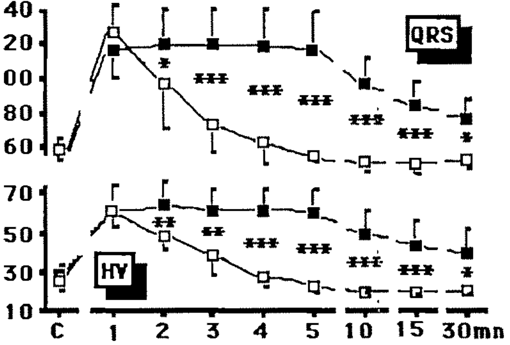
LEMAKALIM REVERSES VENTRICULAR CONDUCTION IMPAIRMENT INDUCED BY A LARGE DOSE OF BUPIVACAINE IN ANESTHETIZED DOGS

JE. de La Coussaye, JJ. Eledjam, P. Bruelle, P. Peray,
A. Sassine.
Departments of Anesthesiology, and of Biostatistics,
University Hospital of Nîmes Laboratory of
Cardiovascular Physiology, Medical School of
Montpellier, France.

Background and goal of study: Large doses of bupivacaine (B) induce dramatic slowing of ventricular conduction which facilitates the occurrence of conduction block and reentrant arrhythmias (1). It is established in anesthetized dogs that a large dose of B induces marked His-Ventricular interval (HV) lengthening, QRS widening and decrease in $LVdP/dt_{max}$ (2). As we previously observed in dogs that lemakalim (L), a potassium channel opener, shortened HV and QRS, the aim of the study was to analyse the effects of L in dogs given a large dose of B.

Materials and methods: Twelve anesthetized and mechanically ventilated mongrel dogs were allocated in 2 groups (n=6). In addition to ECG lead 2, His bundle electrogram via a bipolar electrode and left ventricular and aortic pressures via a double high fidelity micromanometer were recorded. All dogs were given 0.2 mg/kg iv atropine and then 4 mg/kg iv B over 10 s. Group 1 was the control group. In addition, group 2 was given 0.03 mg/kg iv L from 1 mn to 2 mn after B injection. The monitored parameters were: Sinus cycle length (RR, msec), QRS duration (msec), atria-his (AH) and HV intervals (msec), QTc interval, mean aortic pressure (MAoP, mmHg) and the first derivative of systolic left ventricular pressure ($LVdP/dt_{max}$, mmHg/s). There were recorded before B injection (C) and then 1, 2, 3, 4, 5, 10, 15 and 30 min after B injection. Data were expressed as mean ± SD and 2-w.ANOVA (repeated measures) + contrast were used.

Results and discussion: B induced significant RR, AH, HV and QTc lengthening, QRS widening, and decrease in MAoP and in $LVdP/dt_{max}$. Fig shows that L significantly improved B-induced QRS and HV changes. L also significantly shortened QTc. RR, AH, MAoP and $LVdP/dt_{max}$ were not significantly modified by L.



■= Bupivacaine; □= Bupivacaine + Lemakalim;
* p<.05, ** p<.01, *** p<.001

Conclusion: L reversed B-induced ventricular conduction and repolarization impairments in anesthetized dogs and could protect against reentrant arrhythmias.

References: La Coussaye JE, et al: (1) Anesthesiology 1992;77:132-141, (2) Can J Anesth 1992;39:912-918

A.122

MOTOR BLOCKADE AND ABSENCE OF LOCAL NERVE TOXICITY INDUCED BY LIPOSOMAL BUPIVACAINE INJECTED INTO THE AXILLARY BRACHIAL PLEXUS OF RABBITS.

Franz J. Legros, Noelle Lafont, Michel Donnay, and Jean Boogaerts.
Laboratory of Physiopathology, Free University of Brussels, Brussels, Belgium.

Background and goal of study: Bupivacaine has been encapsulated into multilamellar liposomes in order to reduce its systemic toxicity (1) and to lengthen its action. Low, constant and sustained plasma levels have been observed after epidural and axillary brachial plexus injection. The motor block effect and the possible neurotoxicity of liposomal bupivacaine applied *in vivo* to intact peripheral nerve bundles were studied in rabbits.

Materials and Methods: Five milliliters of sterile solutions containing 0.75% bupivacaine encapsulated in 42.5 and 85 mg of multilamellar liposomes made of phosphatidylcholine and cholesterol in a molar ratio 4:3 were administered to rabbits at the level of the brachial plexus located using a seeking electrode to elicit motor movement of the paw. Same doses of empty vesicles were given to control animals. The rabbits were put on the floor at 20-min intervals after injection, and an attempt was made to walk them.

Results and discussion: An immediate motor blockade of the fore limb lasting for 10 hours was measured after injection of the liposomal drug. Empty liposomes did not induce motor block. No animal developed permanent hind limb paralysis. Electron microscopy analysis of the nerves after 2 and 7 days showed no changes of the myelin sheaths and no alteration of unmyelinated fibers after injection of liposomal bupivacaine or empty liposomes

Conclusion: The pharmacologically active liposomal formulation of bupivacaine did not induce any neurological deficit nor alterations of the local nerve tissues.

References: 1. Boogaerts J, Declercq A, Lafont N et al. Toxicity of bupivacaine encapsulated into liposomes and injected intravenously. Comparison with plain solutions. Anesth Analg 1993; 76: in press.

A.123

THE EFFECTS OF BUPIVACAINE, MEPIVACAINE AND PRILOCAINE ON PLATELET AGGREGATION

Nurettin Bayhan, M Erdal Güzeldemir, Hülya Türkan

Department of Anaesthesia and Intensive Care,
Gülhane Military Medical Academy and Faculty,
Ankara, Turkey.

Background and goal of study: Venous thromboembolism is a common postoperative complication (1). The factors involved are complex and their mechanisms have not been exactly elucidated. It was found that blood loss in patients receiving extradural analgesia was decreased significantly. The inhibitory effects of different kinds of local anaesthetics have been reported (2). In this study, the effects of bupivacaine, mepivacaine and prilocaine on platelet aggregation were studied.

Materials and methods: The study included 33 patients, 11 for each agent, in whom elective surgery was performed under extradural anaesthesia. None had any haematological disease. For two weeks before study, the patients had received no medication and no premedication was given. After inserting an extradural catheter, 100 mg bupivacaine, 400 mg mepivacaine or 400 mg prilocaine were administered to achieve extradural anaesthesia. Blood samples were obtained before inserting the extradural catheter and one hour after the anaesthetic agent had been given. Surgery was delayed until after the one hour sample was taken, and no drugs or fluids were given during that hour. For measurement of platelet aggregation, the Sigma protocol was used.

Results and discussion: ADP, collagen, epinephrine and PAF (platelet activating factor)-induced platelet aggregation were not decreased by local anaesthetic agents.

Conclusions: In contrast to previous reports on this subject, bupivacaine, mepivacaine and prilocaine have no effect on platelet aggregation when used for extradural anaesthesia in conventional doses.

References: (1) Cotta AW, et al: Platelet aggregation and pharmacology of local anaesthetics. Drugs Expt Clin Res 1986; XII (9/10): 853. (2) Borg T, Modig J: Potential antithrombotic effect of local anaesthetics due to their inhibition of platelet aggregation. Acta Anaesthesiol Scand 1985; 29: 739.

A.124

THE EFFECTS OF EPIDURAL AND SPINAL ANESTHESIA ON THE CHANGES IN THE PLETHYSMOGRAPHIC SIGNAL IN THE LOWER AND UPPER LIMBS

Sergei Preisman, Ilan Eldar, Azriel Perel

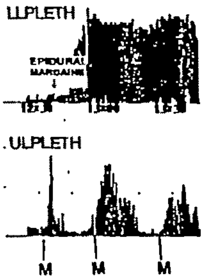
Department of Anesthesiology, Sheba Medical Center, Tel Hashomer, Israel [Sackler School of Medicine, Tel Aviv University.]

The onset of sympathetic block after regional anesthesia is characterized by vasodilation. The resulting increase in peripheral blood flow can be detected by the change in the plethysmographic signal (PLETH) of the anesthetized limb (1). We therefore attempted to examine the following questions: a) Will 1 ml of .5% spinal marcaine (marc) produce a significant change in the PLETH? b) Can the response of the PLETH differentiate between epidural and spinal anesthesia? c) Can the ratio of the PLETH of the upper to lower limb be of help in determining the onset of the sympathetic block?

Twenty five ASA 1-2 patients (mean age 67, range 19-91 years) scheduled to undergo urological (23), orthopedic (1) and general (1) procedures were monitored by two sensors of pulse oximeters (Datex Helsinky, Finland) that were placed on the thumb and second toe. The PLETH display of these monitors allows the measurement of the true PLETH amplitude. After two minutes of baseline monitoring in the sitting position, an epidural (18.7 ± 1.4ml of 0.5% marc) (n = 11) or spinal (2.4 ± 0.2 ml of 0.5% marc) (n = 14) blocks were performed. Four of the patients in the spinal group received one ml of 0.5% marc, followed by the rest of the dose after 3 minutes. After the termination of injection all patients were brought to the supine or lithotomy position. Sedation included 1-2 mg of IV midazolam (M) on demand during the procedure. At the termination of surgery the trended PLETH were recorded by a video printer and analyzed.

One ml of 0.5% marc did not change in the lower limb (LL) PLETH. There was no difference in the latency (time from injection to beginning of change of PLETH) between spinal (5.1 ± 4.2 min) and epidural (4.5 ± 2.3 min), and in the time to peak response (spinal 21.9 ± 16.3 vs epidural 31.5 ± 18.9 min, P < .1). The LL PLETH increased by 790 ± 1522% after spinal, and by 787 ± 415% after epidural, relative to baseline PLETH amplitude. In 8\14 patients in the epidural and 5\11 in the spinal group upper limb PLETH did not change or decreased. In the other patients it increased significantly especially after IV midazolam (M) (see Fig).

The intrathecal administration of 1ml of marc did not produce any changes in the LL PLETH. Thus monitoring LL PLETH cannot allow the reduction of the dose of marc currently used as a "test dose" during epidural block. The LL PLETH could not distinguish between spinal and epidural blocks, mainly due to the variable status of the peripheral circulation in our elderly patient. Although the response of upper limb PLETH was extremely variable, it proved useful as an indirect measure of sedation.



1. Anesth Analg. 1988;67:356

A.125

THE EFFECT OF PARENTERAL DICLOFENAC AND MORPHINE ON EFFICACY DURATION AND HEIGHT OF BLOCKADE DURING CONTINUOUS EPIDURAL BUPIVACAINE 0.5%.

D Forbes, A Binning, NB Scott

Division of Anaesthesia, Glasgow Royal Infirmary, Scotland

Background and goal of study: Postoperative pain involves an increase in afferent input from the wound to the spinal cord with time, which may be reduced by intramuscular diclofenac given preoperatively and continued postoperatively. This may prolong the duration of epidural blockade, in addition to improving pain relief. Systemic morphine has been shown to enhance quality and duration of epidural bupivacaine. The purpose of this double-blind randomised trial was to determine (a) whether intramuscular diclofenac could influence the duration of continuous epidural bupivacaine 0.5% and (b) whether intravenous morphine altered the height of epidural blockade during a continuous infusion.

Patients and methods: In 26 hysterectomy patients (ASA 1-3) a block to T4 was established preoperatively and a continuous infusion of 0.5% bupivacaine 8 ml/h ran for 14 h. 13 patients received diclofenac im and 13 im saline. Height of blockade and pain scores on a 5-point scale were measured hourly. If the block regressed to T10 and/or the pain score was 2 or more, 10 mg of morphine was given intravenously and the height of the block reassessed. 16 patients received morphine in this manner.

Results: Age, weight and loading dose of bupivacaine 0.5% were similar in the two groups. Although duration of blockade was not significiantly prolonged (p=0.087), pain scores were significantly reduced by the use of im diclofenac (p=0.0087). Intravenous morphine (10 mg) did not alter the height of epidural blockade.

Conclusion: Epidural bupivacaine and im diclofenac appeared to act additively on postoperative pain.

References: Lund C, et al: Systemic morphine enhances spread of sensory analgesia during postopérative epidural bupivacaine infusion. Lancet 1985, ii 1156-7.

Bigler D, et al: Tachyphylaxis during postoperative epidural anaesthesia - new insights. Acta Anaesthesiol Scand 1987; 31:664-5.

A.126

NINE YEARS OF CLINICAL EXPERIENCE WITH 29 GAUGE SPINAL NEEDLES

Martin Dittmann, Hans-Gerhard Schäfer,
Felix Renkl, Imrich Greve

Department of Anaesthesia and Intensive Care,
Kreiskrankenhaus, D-7880 Bad Säckingen,
Germany

Background and goal of study: 29 - gauge Quincke needles reduce the incidence of postspinal headache, but are said to be difficult to use, especially for trainees. The introduction of these needles into routine practice has allowed an assessment of their performance in a large series of patients.
Material and methods: 2293 patients receiving spinal aneasthesia were prospectively and blinded studied in a period between 1983 until 1992. All patients were followed up 3 - 5 days after surgery by an anaesthesiologist not involved in giving the spinal anaesthetic. The difficulties encountered by trainees were assessed.
Results and discussion: The overall incidence of postspinal headache was 1,2 % . The highest rate was found in the age group 30 - 39, when it was 2,5 % . No great technical difficulties were encountered and trainees became adept in its use within 6 - 8 weeks .
Conclusion: 29 - gauge spinal needles are suitable for routine use and are associated with a low incidence of postspinal headache.

Reference: Tourtellote W, et al: A randomized double-blind clinical trail comparing the 22 versus 26 gauge needle in the production of the postlumbar puncture syndrome in normal individuals. Headache 1972; 12: 73 - 79.
Dittmann M, et al: Anatomical re-evaluation of lumbar dura mater with regard to postspinal headache. Anaesthesia 1988; 43: 635 - 637.

A.127

INCIDENCE OF POST DURAL PUNCTURE HEADACHE IN YOUNG ADULTS BY THE USE OF THE SPRÔTTE NEEDLE: 300 PATIENTS.

C. Descraques,G. Mion, Y. Auroy,B. Lenoir,B. Pats,B. Rouvier,J.P Chabanne

Department of Anaesthesiology, BEGIN Military Hospital Saint-Mandé, France.

Introduction: The configuration of the needle tip is an another approach to reduce the incidence of post dural puncture headache (PDPH) [1]. The Sprötte needle has been use for 4 years in our department and its use is associated with a low incidence of PDPH. The purpose of this study is to verify prospectively the low incidence of PDPH in young patients by the use of this needle.

Materials and methods: After obtaining informed consent and approval from the hospital Ethics committee, we evaluated 300 patients (264 males and 36 females) undergoing spinal anaesthesia for 262 orthopaedic operations and 38 visceral operations. The mean age was 29 ± 9 years (aged 18-50 years), the height was 175 ± 7 cm and the weight was 73 ± 11 kg. The needle was inserted by a physician 111 times and an anesthest nurse 189 times. The introducer needle was inserted in sitting position (268 times) or in lateral position (32 times). The diameter of the needle was 24G (284 times) or 22G (16 times). The local anesthesic was hyperbaric bupivacaïne 280 times(14,5 mg ± 2 mg) or hyperbaric xylocaïne 20 times (85,3 mg ± 2,9 mg). The patients were hydrated with 602 ml ± 253 ml lactated Ringer' s solution and no abundant hydration was prescribed postoperatively. The patients were questioned every day by an anaesthetist for headaches until the exit from hospital. A headache was considered to be a PDPH if it was postural in character.

Results: The puncture has been single (249 times),double (34 times) or multiple (17 times) with a mean of 1,27 ± 0,69. The incidence of failed anaesthesia has been 4,7 % (all received general anaesthesia). The patients started to get up the 1,0 ± 0,3 day and were questioned during 3,8 ± 1,7 days. Among the 23 headaches we observed, 8 were due to PDPH. They were moderate and responded to bed rest and analgesics. The average duration was 2 days but one headache occurred within 20 days and lasted 1 month[2].

Conclusion: The spinal anaesthesia is easy to perform in 93,7 % of cases with the Sprötte needle which is characterised by a blunt ogival tip and a lateral orifice [3]. This needle is associated with a low incidence of PDPH (2,7%) in young adults and allows a wider use of spinal anaesthesia on this population.

References: 1.Sprötte G, Schedel R, Pajunk H: Regional anaesthesie, 1987,10: 104-108.
2. Descraques C, Mion G: Ann Fr Anesth Reanim, 1992,11/5: 609-610
3. Gielen M: Reg anesth, 1989, 14: 101-106.

A.128

POSTDURAL PUNCTURE HEADACHES ARE NOT RELATED TO THE DURATION OF SPINAL CATHETER PLACEMENT

N. Liu*, A. Montefiore**, N. Kermarec*, L. Beydon*, F. Bonnet*,
*Anesth. Dept., Henri Mondor Hospital, 94010 Créteil,
**Tenon Hospital, Paris-France

Introduction : Continuous spinal anesthesia (CSA) is commonly performed with large sized needles. The resulting dural hole may be responsible for postdural puncture headache(PDPH). Recently Denny et al.[1] have suggested that spinal catheter placement prevented PDPH due to a local oedema which searled the hole after catheter removal. The current study was conducted to assess the incidence of PDPH after CSA and the preventing role of keeping the catheter in place.

Material and Methods : 87 patients scheduled for lower limb orthopaedic surgery were included in this prospective study after informed consent and approval from our ethical committee. CSA was performed with a 18G Tuohy needle allowing the insertion of a 20G spinal catheter. Incremental doses of isobaric 0.5% bupivacaine were injected. At the end of the surgical procedure, patients were allocated randomly into 2 groups. In group 1 the catheter was removed immediately. In group 2 the catheter was removed 12 to 24 hours later. Postoperatively, patients were asked for headache twice a day during the first 3 postoperative days and on the 8th day. Statistiscal analysis used the Student's t-test, the Chi-square test, and the Dunnet and Gent Chi-square test when appropriate; $p<0,05$ was considered significant.

Results : The 2 groups were comparable for demographics (mean ages: 68.5±13.9 and 71.2±9.6 years respectively in groups 1 and 2), total amount of fluids infusion, and postoperative analgesic requirements. Duration of catheter placement was 4.0±1.8 hour and 22.7±4.0 hour in groups 1 and 2 ($p<0,01$). Typical PDPH occured in 8 patients (9.2%), 5 in group 1 and 3 in group 2 (NS). One patient (group 2) required a blood patch, the other patients were treated with analgesics and bed rest. The two therapeutic alternatives were equivalent for prevention of headache ($p<0,05$).

Discussion : Compared to previous data[1] this prospective study documents a higher incidence of PDPH after CSA. Although this study does not completely exclude any effect of the catheter it seems to be of no clinical significance. The hypothesis of an oedema induced by the catheter placement and occluding the dural hole is not supported by these results.

1/ Denny et Coll, Anesth Analg, 66791-794, 1987.

A.129

EPIDURAL BLOOD PATCH FOR TREATMENT OF POSTDURAL PUNCTURE HEADACHE

Per H. Rosenberg, Tomi Taivainen, Mikko Pitkänen, Marjatta Tuominen

Department of Anaesthesia, Surgical Hospital, University Central Hospital, Helsinki, Finland

Background and goal of study: Epidural blood patch (EBP) has gained wide acceptance as a treatment of choice for postdural puncture headache (PDPH). However, the optimal volume of blood for a patch has remained controversial. There are only a few studies concerning the long-term-effects of EBP [1-2]. Our goal was to evaluate the efficacy of different volumes of EBP for treatment of PDPH.

Materials and methods: 81 consecutive patients with PDPH were studied prospectively in two parts. In Study part I 10 ml of blood was injected for EBP in 28 patients. In Study part II the patients received randomly either an amount of 10 ml (27 patients), or 10-14 ml (26 patients) according to the height of the patient. EBP was considered initially successful if PDPH disappeared completely during the 2-h recovery room follow-up. To evaluate the long-term success a questionnaire was mailed to all patients 4 weeks after EBP. The statistical analyses consisted of Student t-test and chi-square test.

Results and discussion: The EBP performed 3.7±2.9 (mean±sd) days following the dural puncture, was initially successful in 88-96% of the patients in different study groups. In the questionnaire, however, only 50-68% of the patients reported that PDPH had disappeared immediately without recurrence. In 16-36% of the patients the PDPH returned at lesser intensity and in 14-17% PDPH was reported to have continued, disappearing gradually. However, 87% of patients were satisfied with the EBP treatment. There were no statistically significant differences between the groups. The results indicate that a larger height-adjusted volume of blood for EBP in adults does not produce a better effect on PDPH compared to a standard 10 ml volume.

Conclusion: Our results indicate that a larger volume of blood than 10 ml for EBP has no therapeutic benefit in the treatment of PDPH. Therefore, we recommend the volume of 10 ml of blood for routine EBP therapy.

References: 1. Abouleish E, et al: Long term follow-up of epidural blood patch. Anesth Analg 1975; 54: 459-463.
2. Tarkkila PJ, et al: The subjective complications and efficiency of the epidural blood patch in the treatment of postdural puncture headache. Reg Anesth 1989; 14: 247-250.

A.130

SEQUENTIAL SPINAL PERIDURAL ANAESTHESIA FOR GYNAECOLOGICAL SURGERY UNDER LAPAROSCOPY

Stéphane Joos, Richard Quintilla, Roland Servais

Clinique Champeau, Beziers, France

INTRODUCTION : loco-regional anaesthesia technics for laparoscopy are generally considered as unsatisfactory. Shoulder pain and respiratory problems are the main disadvantages. The recent clinical availability of 29 G needles for the combined spinal-peridural technic permits a new approach of the anaesthetic management for laparoscopic procedures in young healthy people.

METHOD : after written informed consent 50 females between 25 and 40 years, scheduled for gynaecological surgery under laparoscopy benefited from a combined spinal-epidural technic. After puncture between L2-L3 and detection of the peridural space,spinal anaesthesia was realised with a 29 G needle introduced through the peridural needle in the subarachnoid spaces. A mixture of 50 mg xylocaine 5 % 1cc, bupivacaine 0,25 % plain 10 mg 4cc and sufentanil 7,5 mcg was administered intraspinally. All patients were awake (n:14) or under extremely light sedation (n:36) and breathing oxygen by mask. The following variables. were recorded : 1° - Evaluation of clinical efficacy of the anaesthesia. 2° - the haemodynamic and respiratory repercussions during the procedure by measuring : pulse - BP - oxygen saturation and blood gasses. 3° -post operative complications.

RESULTS : the results were excellent in 94 % of all cases and directly related to the level of anaesthesia (T2-T3). The haemodynamic changes after preventive administration of 1.000 ml of Ringer Lactate and 30 mg ephedrine were unsignificant. No clinical respiratory depression was noted. Oxygen saturation remained higher than 94 %. There was no significant change in Pa02. Even after more than 45 min C02 insufflation pH and PC02 mean modifications did not exceed respectively 1% and 14% of the preinsufflation values.

DISCUSSION : the good results are probably due to the excellent quality of the abdominal relaxation obtained by the spinal anaesthesia combined with the elective action of sufentanil on visceral pain. The insuflation rate however must be slow and the intra-abdominal insuflation pressure kept below 12 mmHG.

CONCLUSION : provided the patient is well informed, sequential spinal peridural anaesthesia is suitable for gynaecological surgery under laparoscopy and offers all the advantages of the loco regional anaesthesia technics.

REFERENCES: 1 J. Gyneccol.Obstet.Biol.Reprod.1991,20,355-360.
2 British Journal of Anaesthesia 1992;68.211-213

A.131

SUBARACHNOID ANAESTHESIA (SAA) AND POST-OPERATIVE ANALGESIA WITH BUPIVACAINE (BV) PLUS FENTANYL (FN) IN GERIATRIC PATIENTS

D Fernandez, C Castells, M Rue, M Bernaus, MM Puig*

Depts of Anaesthesiology, Hospital de Sabadell
and *Hospital del Mar, Autonomous University
of Barcelona, Spain

The aim of the present study was to establish the characteristics of the association of BV with FN when used during SAA in geriatric patients.

Methods: Forty ASA II-III patients (71-86 y.o.) scheduled for total knee (TKR) or hip (THR) replacement under SAA entered the study. They were randomly distributed in two groups which received in a double blind manner, hyperbaric BV (12.5 mg) with (group II) or without FN (25 ug, group I) in a final volume of 3 ml. Institutional and individual consents were obtained. All patients were evaluated prior to surgery for: associated pathology and medication, chronic pain (VAS, Lattimen) and mental status (Eysenck, Hamilton, MMSE). SAA was given at L3-4 with a 22G needle; motor\sensory block, and side effects (respiratory depression, pruritus, nausea and vomiting and hypotension) were recorded intra-op. In recovery room, acute pain (VAS; facial expression test, FET) and MMSE were evaluated at the time of analgesic request (AR).

Results: There were no significant differences between groups regarding: demographic distribution, pre-op and post-op physical and mental evaluation, characteristics of SAA, duration of surgery and time of AR request. Global incidence of side effects was not statistically different among groups; however, the % of patients with pruritus (0 Vs 21.1%) was significantly higher in group II (p<0.05).

When intensity of pain (VAS, FET) was compared according to type of surgery, patients who received FN (group II) had significantly less pain at the time of AR. The results are shown in the Table

	VAS	FET	N
THR (I)	58.5+9.3	6.1+0.4	11
THR (II)	32.1+8.1*	5.2+0.6	12
TKR (I)	79.8+8.6	7.1+0.2	9
TKR (II)	37.5+12.9**	4.5+0.5**	8

*p<0.05 and **p<0.01 when compared to the same type of surgery in group I (N=number of patients)

Conclusions: Our results indicate that in geriatric patients, the association of BV and FN during SAA:

a) Improves post-operative analgesia

b) Does not alter the duration of motor/sensory block induced by BV

c) Increases intra-op pruritus

d) Does not alter the mental status of the geriatric patients.

A.132

FENTANYL OR BUPRENORPHINE SIDE EFFECTS IN SPINAL ANAESTHESIA

Roberta Foppoli, Paolo Lunghi, Zeffiro Bonara, Carla Mora, Raffaele Stacca .

**Department of Anaesthesia and Intensive Care
Carpi Italy**

Background and goal of study: The aim of this study was to compare the complication rate between two groups of elderly patients undergoing orthpaedic surgery using subarachnoid anaesthesia with hyperbaric bupivacaine and fentanyl or bupivacaine and buprenorphine.

Materials and methods: The study was conducted on 70 patients , 49 females and 21 males (ASA II - IV), with a mean age of 83.5 ± 5 years. Patients were randomised into two groups: the first (group B) received hyperbaric bupivacaine 1% 15 mcg/ kg and buprenorphine 2 mcg/kg, the second (group A) hyperbaric bupivacaine 1% at the same dosage as group B and fentanyl 1 mcg/kg. Spinal anaesthesia was performed at the L 3/4 level using a 25G Whitacre needle.

Results: Within the first hour, hypotension was observed in 11.4 % (4 patients) in group A , and in 46% (16 patients) in group B. Nausea and vomiting was not observed in group A, while one patient suffered from these problems in group B. Pruritis (of the trunk) was observed in three patients in group A and none in group B.

Conclusions: Buprenorphine/bupivacaine was associated with a higher incidence of hypotension than fentanyl/bupivacaine but caused less pruritis.

A.133

COMPARISON BETWEEN DOUBLE-BURST STIMULATION AND 50, 100 HZ TETANIC FADE DURING SPONTANEOUS RECOVERY OF VECURONIUM INDUCED NEUROMUSCULAR BLOCKADE

Michel J. Baurain, Boris S. Dernovoi, Alain A. d'Hollander, Denis M. Schmartz.

Anesthesiology Department, Hopital Erasme, Free University of Brussels, 1070 Brussels, Belgium.

Introduction: During recovery, tactile evaluation of the response to Double Burst Stimulation (DBS$_{3,3}$)[1] is superior to tactile evaluation of the response to train-of-four (TOF) stimulation[2]. The clinical perception of a sustained response to DBS stimulation does not always ensure adequate neuromuscular recovery as defined by a sustained response to 50 Hz tetani[3]. The purpose of this study is to compare DBS$_{3,3}$ to TOF, 50 and 100 Hz tetanic fade during spontaneous recovery of vecuronium induced neuromuscular blockade.

Methods and materials: Fourteen ASA I-II adult anesthetized (thiopental, fentanyl, N_2O) patients (with informed consent and approval by the Research Committee, Brussels Free University, Brussels, Belgium), undergoing elective surgery, were monitored (isometric adductor pollicis mechanical activity). Neuromuscular block was produced by vecuronium 100 µg/kg and additional doses of 20 µg/kg. At the end of surgery, the following variables were observed: twitch height was measured every 10 s and TOF (2Hz), every 3 min until TOF spontaneously regained 70%. 20 s later, a DBS was assessed ,followed by tetanic fade (50 and 100 Hz, 5 s duration, 1 min apart, sequentially assessed in a random fashion). Statistical analysis of the data was performed with the Wilcoxon Matched-pairs Signed-ranks Test, according to SPSS package programs. The comparisons were considered significant at 0.05 level.

Results: All results are summarized in table 1. When TOF ratio spontaneously regained 71±1%, DBS value (86%) is significantly lower than 50 Hz tetanic fade (92%), but higher than TOF ratio (71%) and 100 Hz tetanic fade (48%).

Conclusion: During spontaneous recovery of vecuronium induced paralysis in young anesthetized patients, DBS is more sensitive than 50 Hz tetanic fade but less sensitive than 100 Hz tetanic fade and TOF ratio to detect slight residual neuromuscular blockade, evidenced with instrumental recordings in place of purely clinical assessment.

References: 1. Engbaek J.Br J Anesth, 62: 274-278, 1989
2. Drenck NE. Anesthesiology, 70: 578-581, 1989
3. Anderson EP. Anesthesiology, 73: A 880, 1990

Table 1

Values of TOF, DBS, TF50, TF100 (MEAN ± SEM)(n=14)

T.O.F.%	DBS(1)%	T.F.50%	T.F.100%
71 ± 1	86 ± 2	92 ± 4	48 ± 5

└── ** ──┘ └── * ──┘

└──── *** ────┘

Statistically significant differences: *p<0.05, **p<0.01, ***p<0.001

A.134

REVERSAL OF VECURONIUM INDUCED NEUROMUSCULAR BLOCKADE: NO EFFECTS OF ATROPINE ADMINISTRATION TIMING.

Michel J. Baurain, Boris S. Dernovoi, Alain A. d'Hollander, P.C. Bollen.
Anesthesiology Department, Hôpital Erasme, Free University of Brussels, B-1070 Brussels, Belgium.

Introduction: Atropine is commonly used to block undesirable muscarinic effects of the anticholinesterase agents. The results observed in man[1] and cats[2] seem indicate that atropine may interfere with the neuromuscular junction. This study investigates this role in human clinical anesthesia, when atropine is given either simultaneously or prior to neostigmine administration to reverse a vecuronium induced paralysis.

Methods and materials: Twenty-four ASA I-II adult anesthetized (thiopental, fentanyl, N_2O) patients, (with informed consent and approval by the Research Committee, Brussels Free University, Brussels, Belgium), undergoing elective surgery, were monitored (isometric adductor pollicis mechanical activity). Neuromuscular block was produced by vecuronium 100 µg/kg and additional doses of 20 µg/kg. For reversal of paralysis, the patients were randomly divided into two groups of 12 patients each and received 15 µg/kg atropine either when twitch tension spontaneously regained 10% of its control value in the first group (TH10) or 25% of its control value in the second group (TH25). All the patients received a fixed dose of 40 µg/kg neostigmine when twitch tension spontaneously regained 25% of its contiol value. After neostigmine administration, the following variables were observed during a 15 min period: twitch height was measured every 10 s and train-of-four (2Hz), every 3 min. Immediately thereafter, tetanic fades -50 and 100 Hz, 5 s duration, 1 min apart- were assessed sequentially in a random fashion. Statistical analysis of the data was performed with the one-way analysis of variance test, according to SPSS package programs. The comparisons were considered significant at 0.05 level.

Results: All results are summarized in table 1. There are no significant differences between the two groups, for all the observed tests.

Conclusion: In the present study, atropine administration prior to neostigmine does not improve the neostigmine recovery from a vecuronium-induced neuromuscular blockade. In these clinical conditions, atropine administration timing appears of limited importance to optimize the reversal of neuromuscular transmission impairment in young anesthetized patients.

References:
1. Baurain MJ. Anesthesiology, 73: A896, 1990
2. Alves-Do-Prado. Anesth Analg, 66: 492-496, 1987

Table 1: Evolution of the T.H., T.O.F., T.F. 50 T.F 100 at the 15th min (Means % ± SEM)

Group	T.H.	T O.F	T.F. 50	T F 100
TH10	96 ± 1	87 ± 2	92 ± 1	78 ± 2
TH25	97 ± 1	89 ± 2	94 ± 1	81 ± 4

A.135

CAN REPETITION OF HIGH FREQUENCIES STIMULI ALTER THE VALUE OF 50 AND 100 HZ TETANIC FADE DURING VECURONIUM INDUCED NEUROMUSCULAR BLOCKADE?

Michel J. Baurain, Boris S. Dernovoi, Alain A. d'Hollander, Denis M. Schmartz.

Anesthesiology Department, Hôpital Erasme, Free University of Brussels, B-1070 Brussels, Belgium.

Introduction: Tetanic stimulation may condition subsequent low frequencies stimuli responses for a period of 6-30 min. Repeated administration of tetanic stimuli may demonstrate a false recovery from muscle relaxants[1]. Train-of-four (TOF) ratio and double-burst stimulation (DBS) returned to baseline within 2 min after a 5-s, 50-100 Hz tetanic stimulus[2]. A period of 5 min between sequential 50 Hz tetanic stimuli would be sufficient to ensure accurate assessment of tetanic amplitude or fade[3]. This study investigates possible conditioning of tetanic stimuli upon high frequencies (50 and 100 Hz) stimuli responses for a 1 min interval, either during spontaneous recovery or after neostigmine administration.

Methods and materials: Twenty-one ASA I-II adult anesthetized (thiopental, fentanyl, N_2O) patients (with informed consent and approval by the Research Committee, Brussels Free University, ULB, Brussels, Belgium), undergoing elective surgery, were monitored (isometric adductor pollicis mechanical activity). Neuromuscular block was produced by vecuronium 100 μg/kg and additional doses of 20 μg/kg. Tetanic fade - 50 and 100 Hz, 5 s duration, 1 min apart- were assessed sequentially in a random fashion 2 times at 1 min interval: in the first group (n=11), when TOF ratio spontaneously regained 70%, in the second group (n=10), 15 min after 40 μg/kg neostigmine i.v.. Statistical analysis of the data was performed with the Wilcoxon Matched-pairs Signed-ranks Test, according to SPSS package programs. The comparisons were considered significant at 0.05 level.

Results: There are no significant differences between the values (table 1) of 50 and 100 Hz tetanic fade before and after conditioning, either during spontaneous recovery or after neostigmine administration.

Conclusion: In the present clinical conditions, neuromuscular assessment can be performed by the use of a 5-s, 50-100 Hz tetanic stimulus without distorting subsequent 5-s, 50-100 Hz stimuli responses, after a 1 min period in young anesthetized patients.

References: 1. Viby-Mogensen J.: Anesthesiology, 55: 458-461, 1981
2. Brull SJ.: Anesthesiology, 74: 64-70, 1991
3. Silverman DG.: Anesthesiology, 73: A 865, 1990

Table 1: **Values (%) of 50 and 100 Hz tetanic fade before (I) and after (II) conditioning (MEAN ± SEM)**

Spontaneous recovery (n=11)	
TF 50(I) 92±1	TF 100(I) 48±5
TF 50(II) 92±1	TF 100(II) 47±5
15 min after neostigmine (n=10)	
TF 50 (I) 93±1	TF 100(I) 80±2
TF 50 (II)93±1	TF 100(II) 78±2

A.136

DOES NICARDIPINE POTENTIATE THE NEUROMUSCULAR BLOCK OF ATRACURIUM ?

JE Bazin, T Gillart, A. Comte, C. Dubray, P Schoeffler

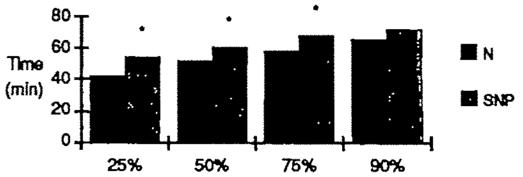
Département d'Anesthésiologie - Hôpital Gabriel-Montpied - 63000 Clermont-Ferrand. France

Nicardipine (N) have been proposed for deliberate hypotension in orthopedic surgery. Howewer, it has been reported that, in vitro and in man, some calcium channel blockers may exacerbate the effect of muscle relaxants (1). The aim of this study was to compare the atracurium neuromuscular block during deliberate hypotension induced either by N or by sodium nitroprusside (SNP) which does not interact with relaxants.

Method : After approval given by the Local Ethic Commitee, and written informed consent obtained, 37 ASA I-II patients, mean age 68.1 ± 9.7 years, scheduled for total hip arthroplasty, were randomly allocated in two groups : group SNP (n = 18) and group N (n = 19). After premedication (midazolam 15 mg PO), anesthesia was induced and the trachea intubated using propofol (2 mg/kg) and fentanyl (2 μg/kg). Anesthesia was maintained with the same drugs (propofol 0.2 mg/kg/min, fentanyl 2 μg/kg/h). The ulnar nerve was stimulated at the wrist with surface electrodes (trains-of-four (TOF) at 20 s intervals). An evoked compound electromyogram of the thenar area was recorded (Datex NMT monitor). Hypotension (MAP 50-60 mmHg) was induced with a SNP infusion (0.5-1.5 mg/kg/min) in group SNP and with N (3-15 mg/h) in the other group. Then atracurium was injected (0.3 mg/kg as a bolus). The average times to 25, 50, 75 and 90 % of TOF ratio recovery were compared in the two groups using ANOVA and Student t-test.

Results : The two groups were similar with regards to age, weight and hypotension level. The data summarized in fig 1 indicate that N does not extend the duration of atracurium neuromuscular block. On the contrary it appears that recovery is faster with N than with SNP.

References : Gomez-Iglesias E. In vivo potentiation of atracurium neuromuscular blockade by nimodipine in rabbits. Acta Anaesthesiol Scand,1992 ; 36 : 67-69



TOF ratio (* : p < 0,05)

A.137

NEOSTIGMINE ANTAGONISM OF NEUROMUSCULAR BLOCKADE INDUCED BY MIVACURIUM, VECURONIUM AND ATRACURIUM.

Boris S. Demovoi, Michel J.Baurain, Alain A.d'Hollander,
P.C.Bollen.

Anesthesiology Department, Hôpital Brugmann and Erasme,
Free University of Brussels, B-1070 Brussels, Belgium.

Introduction: Mivacurium is a new short acting nondepolarizing muscle relaxant[1] hydrolyzed by plasma cholinesterases. Since both these enzymes and the junctional acetylcholinesterase are inhibited by neostigmine[2], this study investigates and compares the neostigmine reversal of mivacurium, vecuronium and atracurium-induced paralysis.

Methods: Forty-two ASA I-II adult anesthetized (thiopental, fentanyl, N_2O) patients (with informed consent and approval by the Research Committee, Free Univ. of Brussels, Brussels, Belgium), undergoing elective surgery, were monitored (isometric adductor pollicis mechanical activity). The patients were randomly divided into 3 groups of 14 patients each and received either mivacurium (Group M: 0.15 mg.kg^{-1} followed by an infusion adjusted to maintain a 5% twitch height (TH)), either vecuronium (Group V: 100 µg.kg^{-1} and additional doses of 20 µg.kg^{-1}) or atracurium (Group A: 500 µg.kg^{-1} and additional doses of 100 µg.kg^{-1}) For reversal of paralysis, the patients received 15 µg.kg^{-1} atropine and 40 µg.kg^{-1} neostigmine when twitch tension spontaneously regained 25% of its control value. After neostigmine administration, the following variables were observed during a 15 min period: TH was measured every 10 s and train-of-four (2 Hz, TOF), every 3 min. Immediately thereafter, tetanic fades -50 and 100 Hz, 5 s duration, 1 min apart- were assessed sequentially in a random fashion. Statistical analysis of the data was performed with the Kruskal-Wallis test. The comparisons were considered significant at 0.05 level.

Results: All results are summarized in table 1. There are no significant differences between the 3 groups, for all the observed parameters.

Table 1: Evolution (%) of TOF and values (%) of TH, TF50 and TF100 15 min after neostigmine. (Mean ± Sem)(* p<0.05)

	Tof0	Tof3	Tof6	Tof9	TofF12	Tof15	TH	TF50	TF100
Miva	8±1	56±3	79±1	88±1	91±1	93±1	96±1	92±1	83±2
Vecu	7±1	68±2	78±2	82±2	85±2	87±2	94±2	93±1	82±4
Atra	8±1	55±3	78±2	86±1	90±1	92±1	98±1	90±1	78±2

Conclusions: Despite different speeds of spontaneous recovery and potential plasma cholinesterases-neostigmine interactions, the reversal obtained after neostigmine administration appears quite comparable for mivacurium, vecuronium and atracurium.

References: 1 .Anesthesiology 68: 723-732, 1988
2. Pharmacology of anticholinesterase drugs, Neuromuscular Junction, 1976, pp 487-581

A.138

THE PHARMACOKINETICS OF ROCURONIUM IN PEDIATRIC PATIENTS: A POOLED DATA ANALYSIS

C Meistelman, P Fiset, B O'Kelly, J Frossard, B Plaud, C Ecoffey

Departments of Anaesthesiology, Hopital du Kremin-Bicêtre, Bicêtre, Institut Gustave Roussy, Villejuif, France and Mc Gill University, Montréal, Canada.

Background and goal of the study: Rocuronium is a new non depolarizing muscle relaxant with a short onset time. The aim of this study was to determine the pharmacokinetics of rocuronium in pediatric patients, particularly whether patient covariates (age, weight, height, body surface area), when added to the model, might improve the quality of the fits.

Material and methods: The study was approved by our Ethical Committee and informed consent was obtained from the parents. Twenty two ASA I or II children (3 months-) were studied. Anaesthesia was induced with N2O and halothane. After intubation without muscle relaxant, anaesthesia was maintained with N2O and an age-adjusted end-tidal concentration of halothane (1 MAC). All the patients were ventilated mechanically, when anaesthesia was stable, rocuronium 0.8 mg/kg was injected as a bolus.Venous blood samples were drawn 1, 3, 5, 10, 15, 20, 30, 60, 120, 180, 240 and 360 minutes after injection. Rocuronium plasma concentrations were determined by HPLC, the lower limit of quantification was 5 ng/ml. An extended least squares non-linear regression program (MK-Model) was used to simultaneously fit the observations for all 22 children to a single estimate of the pharmacokinetic parameters for the entire population. Patients covariates were added to the model to determine their effects. The models were analyzed by comparison of log likelihoods. If the addition of a single covariate to a parameter improved the log likelihood by > 4, then the improvment was considered statistically significant.

Results and discussion: The pharmacokinetics of rocuronium was described by a two compartment model. The inclusion of weight and age as covariates resulted in a statiscally significant improvment of the fits. The inclusion of Body Surface Area instead of weight, did not statistically improve the log lokelihood. The results are summarized in Table 1. In the proportional model, all the parameters were proportional to weight. In the age-adjusted model, only V2 and Cl1 reflected an influence of age. The absolute performance error (APE) of the model was defined as [%PE]= [100(measured-predicted)/predicted].

Conclusion: Among the covariates, the use of age or weight give the best improvment to describe rocuronium pharmacokinetic parameters in the pediatric population.

Reference: Shafer SL et al. Anesthesiology 1990; 73:1091-1102.

Table 1: Pharmacokinetic parameters. V1: central volume; V2: peripheral volume. CL1: central clearance; CL2: peripheral clearance. wt:weight in kg; age in years.

	Proportional Model	Age-adjusted Model
V1 (l)	.12*(wt)	.12 * wt
V2 (l)	.19*(wt)	.026*(wt)+.4*age+.8
Cl1 (ml/min)	5.9*(wt)	2.2*(wt)+14.6*age+14
Cl2 (ml/min)	4.8*(wt)	4.0*(wt)
median APE(%)	24	22

A.139

PRIMING OF ATRACURIUM WITH MAGNESIUM

E Lampl, M Dandoy

Department of Anaesthesiology, CHNO des quinze-vingts, 28 rue de Charenton, 75012 Paris, France

Background and goal of study: Magnesium potentiates depolarizing and non-depolarizing muscle relaxants (1). We studied the effect of pretreatment with magnesium sulphate ($MgSO_4$) on the neuromuscular block produced by atracurium.

Materials and methods: After approval by the human ethics committee, ASA I or II consenting patients scheduled for ophtalmic surgery were randomly allocated to two groups of 15 each. The study was double-blind. All patients were premedicated with hydroxyzine 2 $mg.kg^{-1}$ and anaesthetized with fentanyl 2 $\mu g.kg^{-1}$ followed by propofol given till loss of the eye lash reflex. After induction, patients in group A received $MgSO_4$ 0.25 $mmol.kg^{-1}$ over one min. Patients in group B received a similar volume of normal saline. Subsequently, atracurium 0.20 $mg.kg^{-1}$ was given and train-of-four (TOF) response was recorded every ten seconds using an electromyogram (Datex Relaxograph monitor).

Results: Onset time, from the end of injection to $T1<10\%$, was 137.3±21 sec in group A and 228.7±74 sec in group B ($p<0.001$). Duration of muscle relaxation, from the end of injection till T1 becomes again = 25%, was 34.6±9.2 min in group A and 26.3±8.3 min in group B ($p<0.05$). Recovery time, from $T1=25\%$ to $T1=75\%$, was 14.9±4 min in group A and 15.4±3.5 min in group B (NS). T4:T1 ratio during recovery of T1 to 25% was 23.4±10.4% in group A and 24±12.2% in group B (NS). The repercussion of $MgSO_4$ on blood pressure and heart rate (2) was insignificant.

Conclusion: In contrast to what has previously been reported for pancuronium (3), MgSO4 potentiates esentially the onset time of neuromuscular blockade by atracurium.

References: (1) Ghonheim MM, Long JP: The interaction between magnesium and other neuromuscular blocking agents. Anesthesiology 1970; 32:23-7. (2) Vigorito C: Hemodynamic effects of magnesium sulfate on the normal human heart. Am J Cardiol 1991; 67:1435-7. (3) James MFM, et al: Priming of pancuronium with magnesium. Br J Anaesth 1991; 66:247-9.

A.140

SUPRA-ADDITIVITY BETWEEN ATRACURIUM AND VECURONIUM

Olli A. Meretoja, Barbara W. Brandom,
Tomi Taivainen, Larisa Jalkanen

Department of Anaesthesiology, Children's Hospital
University of Helsinki, Helsinki, Finland

Background and goal of study: Supra-additivity (synergism) between some competitive neuromuscular blocking agents of different molecular structure has been observed both *in vivo* and *in vitro* [1-2]. The mechanism of supra-additivity is obscure. No study has evaluated maintenance requirement of relaxant combinations, or recovery of neuromuscular function blocked by these combinations.

Materials and methods: We evaluated three dose-ratio combinations of atracurium and vecuronium (cAV in 10:1, 4:1 and 1.6:1 in μg/μg basis) in 30 patients of 3-10 years of age during thiopentone-alfentanil-N_2O-O_2 anaesthesia. Neuromuscular block was monitored by adductor pollicis EMG. A log-probit dose-response curve of a particular cAV was created and neuromuscular block was maintained by small increments of the same cAV. Spontaneous recovery of the neuromuscular function was also recorded.

Results and discussion: An ED_{95} of a cAV in an equipotent dose-ratio (4:1 in μg:μg basis) was 95 ± 6 μg/kg of atracurium together with 24 ± 1 μg/kg of vecuronium (mean ± SEM) (figure). These dosages constituted 29% of the ED_{95} values of the parent agents and express synergism ($P < 0.0001$). cAV in nonequipotent dose-ratios also expressed synergism but was less potent ($P < 0.001$) (figure). Predominant affinity of a cAV to one α-subunit in the neuromuscular receptor explains the mechanism of supra-additivity. Hourly requirement of any cAV to maintain a 90-95% neuromuscular block was 2.0 ± 0.1 times an individual ED_{95} dose of cAV. Recovery index, time to recover from 75 to 25% neuromuscular block, was 8.9 ± 0.5 min. Both of these values are like those mirroring either atracurium or vecuronium alone. This indicates that a cAV can be regarded as an intermediate-acting neuromuscular blocking agent.

Conclusion: A cAV is supra-additive when compared to parent agents and may reduce drug consumption by 40%.

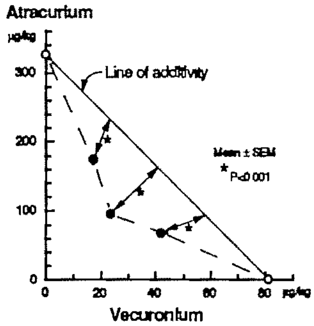


Figure. ED_{95} doses of three different dose-ratio combinations of atracurium and vecuronium (closed circles) and their parent agents (open circles). All combinations are supra-additive, synergistic.

References: [1] Lebowitz PW, et al. Anesth Analg 1980;59: 604-609. [2] Waud BE, et al. Anesthesiology 1985;63:4-15.

A.141

CONCENTRATION-EFFECT RELATIONSHIP AT THE VOCAL CORDS AND THE ADDUCTOR POLLICIS FOLLOWING ROCURONIUM ADMINISTRATION

B Plaud, JH Proost, JMKH Wierda, B Debaene, J Barré,
C Meistelman,
Department of Anesthesiology, IGR, Villejuif, France
University Centre for Pharmacy, Groningen, The Netherlands
Research Group for Exp. Anesthesiology and Clinical Pharmacology, Groningen, The Netherlands
University Department of Clinical Pharmacology, Créteil, France

Background and goal of study: It was recently shown that the adductor muscles of the larynx are more resistant to nondepolarizing muscle relaxants than the muscles of the adductor pollicis (AP) (1). Several factors govern onset, and potency, but no comparative data are available on the pharmacokinetic-pharmacodynamic (PK-PD) relationship between vocal cords (VC) and the AP. The aim of the study was to determine and to compare the PK-PD relationship between the VC and the AP following rocuronium administration.

Materials and methods: The study was approved by the Local Ethical Committee and informed consent was obtained from 8 patients ASA 1-2. Anesthesia was induced and maintained with propofol and alfentanil intravenously. 500 $\mu g.kg^{-1}$ of rocuronium was injected as a infusion over 5 min. Arterial rocuronium concentrations were measured by HPLC 1, 2, 3, 4, 5, 6, 8, 10, 12, 15, 20, 30, 45, 60, 120, 180, 240, and 300 min after the start of the infusion. The lower limit of quantification of the method was 10 $ng.ml^{-1}$. Simultaneously NMB was measured at the VC and the AP after supramaximal TOF stimulation at the recurrent laryngeal nerve and the ulnar nerve. NMB of the VC was assess by pressure change in the cuff of the tracheal tube (2). Pharmacokinetic analysis and PK-PD modelling were performed using PK/PD Fit software. The transfer rate constant (k_{eo}), the half time for equilibration ($t_{1/2e}$), the plasma concentration that results in 50% paralysis (EC_{50}) and the parameter of the Hill equation (γ) were determined using the Sheiner model (3).

Results and dicussion: Results are summarized in table 1. The VC were more resistant than the AP following rocuronium administration and the rate constant k_{eo} was shorter at the VC. The greater k_{eo} at the VC than at the AP might be due to a relatively greater blood flow at the VC than at the AP muscle.

Conclusion: Following rocuronium administration the VC needs more compound to obtain the same effect and the onset of action was more rapid than at the AP.

References:

(1) Can J Anæsth 1992; :39:665-669
(2) Anesthesiology 1991; 74:827-832
(3) Clin Pharmacol Ther 1979; 25:358-371

Table 1:

PK-PD modelling at the VC and the AP.

	k_{eo} (min-1)	$t_{1/2e}$ (min)	EC_{50} ($\mu g.ml^{-1}$)	γ
VC	0.34±0.18	2.3±0.7	1408±175	2.9±1.0
AP	0.20±0.14*	4.4±1.5*	816±187*	4.4±1.4

Results are expressed as mean ± SD.
* = $p < 0.05$ between the two muscles.

A.142

MONITORING THE ONSET OF NEUROMUSCULAR BLOCKADE AT THE ORBICULARIS OCULI CAN PREDICT GOOD INTUBATING CONDITIONS WHEN USING 2 X ED95 OF ATRACURIUM.

B DEBAENE, C MEISTELMAN, F DONATI, A LIENHART.

Department of Anaesthesia, Hôpital Saint Antoine, Paris,
and Institut Gustave Roussy, 94805 Villejuif CEDEX
FRANCE

Background and goal of study: The onset time of neuromuscular blockade at the vocal cords and the orbicularis oculi (OO) is shorter than at the adductor pollicis (AP) (1), and intubation can be performed before maximum blockade occurs at the AP. However vocal cords are more resistant to NDMR than the AP (2). This clinical study was designed to assess if monitoring at the OO can predict good intubating conditions following atracurium.

Materials and Methods: 50 patients were studied after obtaining informed consent. Anaesthesia was induced with thiopental and fentanyl. The ulnar and facial nerves were simultaneously stimulated with train of four (TOF) every 10 sec and the muscular responses were visually recorded. Patients received either atracurium 0.5 mg.kg-1 (n = 30) or 0.3 mg.kg-1 (n = 20). In each group, intubation was randomly performed when the OO (Group OO) or the AP (Group AP) was completely blocked. Complete blockade was achieved when no response to TOF occured. In case of no complete blockade, intubation was performed 5 min after atracurium administration. Onset time (time from injection to complete blockade) was recorded for each muscle and compared using a paired t test. Intubating conditions were scored on a 1 to 4 scale (1 = excellent, 2 = good, 3 = poor, 4 = inadequate) and compared using a CHI square test. All intubations were performed by a physician unaware of the dose and the muscular responses. Results are expressed as mean ± SEM.

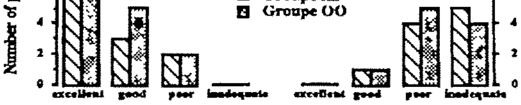
Results ans Discussion: After 0.5 mg.kg-1, complete blockade at the 2 muscles was achieved in all patients. Onset time at the OO was shorter than at the AP (2.35 ± 0.12 vs 3.59 ± 0.15 min respectively, $P < 0.001$). After 0.3 mg.kg-1, it was not possible to compare the onset because complete blockade was achieved only 2/20 at the OO and 12/20 at the AP. Intubating conditions were comparable in both groups: good or excellente after 0.5 mg.kg-1; poor or inadequate after 0.3 mg.kg-1 (figure).

Conclusion: When no response at the OO occur, intubation can be performed safely in all the patients. This information is provided 1.2 min before complete blockade at the AP. This monitoring cannot be useful when using small dose of atracurium because neither OO nor vocal cords are sufficiently blocked.

References :

1- Anesthesiology 1991, A797.
2- Anesthesiology 1991, 74: 833-837.

Figure :



A.143

PREOPERATIVE CLONIDINE IMPROVES POSTOPERATIVE RENAL FUNCTION IN CABG PATIENTS

Kulka, P.J., M.Tryba, C. Menzel, F.Leurs, C.Frankenberg

Department of Anesthesiology, Intensive Care Medicine and Pain Therapy
University Hospital Bergmannsheil, Gilsingstr. 14, 4630 Bochum, Germany

Introduction: In animal studies clonidine (clo) increases urine volume, natriuresis and free water clearance which may be attributable to activation of renal α_2-adrenoceptors (1). This study was undertaken to evaluate the effect of preanesthetic clo-administration on renal function in CABG-patients.

Methods: This study was approved by the local ethical committee. 40 patients scheduled for CABG surgery randomly received 300 µg clo or placebo (pla) 1 hour prior to induction of anesthesia. Anesthesia technique and perioperative fluid therapy were standardized in both groups. For assessment of renal function creatinine clearance was determined between 6.00 p.m. and 6 a.m. the night prior to surgery (T1), after surgery (T2) and 48 hours after surgery (T3). For statistical evaluation ANOVA ($p<0.05$) was performed.

Results: Demographic parameters, duration of surgery, postoperative blood loss, fluid replacement and creatinine clearance prior to surgery (T1: pla: 94 (±25) cc/min; clo: 89 (±19) cc/min) were similar in both groups. At T2 creatinine clearance in clo-patients was significantly higher than in patients of the pla-group (pla: 63 (±17) cc/min; clo: 90 (±15) cc/min). At T3 no statistical difference between both groups could be observed (pla: 80 (±34) cc/min; clo: 90 (±33) cc/min).

Conclusion: The preoperative administration of clo (300 µg) leads to a significant improvement of postoperative renal function. Since fluid therapy was not affected by the administration of clo we hypothesize that this effect is mediated by renal α_2-adrenoceptor.

References: 1. Stanko CK, MI Vandel, DD Smyth: Characterization of alpha(2)-adrenoceptors in the rat: proximal tubule, renbal membrane, and whole kidney. Eur. J. Pharmacol. (1990); 175: 13-20

A.144

EFFECTS OF ORAL PREOPERATIVE GUANFACINE ON ANESTHETIC REQUIREMENTS.

Edgard Engelman, Maurice Lipszyc
Department of Anaesthesia, Erasme Hospital, Brussels, Belgium

Background and goal of the study: In animals, guanfacine, a potent alpha-2 agonist, produces a 100% longer sleeping time than clonidine. As an antihypertensive agent in humans, guanfacine produces less somnolence than clonidine. These conflicting results lead us to perform 2 studies to determine the effects of guanfacine on the amount of enflurane needed to maintain hemodynamic stability during carotid surgery, and on the amount of alfentanil, eventually supplemented with isoflurane, during infrarenal aortic aneurysmectomy.

Materials and methods: In each study 14 patients received 1 mg of guanfacine and 14 patients a placebo tablet in a double blind manner, 90 min. before anesthesia. For carotid surgery, anesthesia was induced with 0.2 mg/kg etomidate. After endotracheal intubation facilitated by 0.1 mg/kg pancuronium, the lungs were ventilated with an O2/N2O mixture (FiO2: 0.5). Enflurane was administered to maintain systolic blood pressure inside the usual preoperative value (baseline value) ± 20% limits. For aortic surgery anesthesia was induced by the injection of 120 mcg/kg of alfentanil and was continued by an infusion of 1.5 mcg/kg/min. To maintain the systolic blood pressure inside the baseline ± 20%, 20 mcg/kg boluses repeated at 2 min. intervals, up to 5 times, were injected; if this was insufficient to control 1 episode of hypertension, isoflurane was added in 0.2% increments. The enflurane or isoflurane concentration was measured using an infrared absorption technique. Heart rate and blood pressure were measured and stored every 5 sec using a computerized system. Plasma norepinephrine concentrations were measured during surgery in 6 guanfacine and 7 placebo patients of the alfentanil study.

Results: The distribution of the values of blood pressure, compared to the baseline values, were statistically identical between the 2 groups during both studies. In the enflurane study, heart rate was lower , and in the alfentanil study there were fewer episodes of tachycardia , in the guanfacine group.

End-tidal enflurane concentration (%) (M± SD) * = $p<0.01$

	Intubation Incision	Incision Clamping	Clamping Unclamping	Unclamping End surgery
Guanfacine	0.56±0.22*	0.71±0.21	0.54±0.13	0.81±0.18
Placebo	0.75±0.22	0.75±0.24	0.59±0.12	0.82±0.17

Alfentanil administration (mcg/kg/min) (M ± SD)

	Bolus dose	Induction Incision	Incision Clamping	Clamping Unclamping	Unclamping End surgery
Guanfacine	117±7.9	3.9±2.9	6.9±4.2	2.6±1.2	3.3±2.2
Placebo	120±2.7	2.8±1.7	5.6±2.3	1.9±1.0	2.8±1.8

There was no statistical difference in the amount of anesthetics administered during surgery between the 2 groups in both studies. The amounts of isoflurane supplementing alfentanil were also identical. Norepinephrine concentrations were lower ($p=0.02$) in the guanfacine group.

Conclusions: This lack of sparing effect could be due to the a2-C10 selectivity of guanfacine, an a2-C4 isoreceptor activity seeming necessary to express an anesthetic-like action.

A.145

PHARMACOKINETICS AND EFFECTS OF I.M. ALFENTANIL AS PREMEDICATION FOR OUTPATIENT CATARACT SURGERY

Timo Ali-Melkkilä, Markku Virkkilä, Helena Soini, Jussi Kanto.
Department of Anaesthesiology, University of Turku and Analytic department, Orion Pharmaceutica. Finland.

Background and goal of study: Although not routinely used in outpatients cataract surgery, a preanaesthetic medication may be useful to some patients, because it alleviates the anxiety and pain associated with the periocular injection of the local anaesthetic. Alfentanil has been shown to reduce pain from 5 to 60 min after i.m. injection and may thus be suitable premedication for short painful procedures, such as periocular block. The goal of the present study was to determine the basic pharmacokinetic features and clinical effects of alfentanil, when injected into the deltoid (D) or gluteal (G) muscle as premedication of periocular anaesthesia in outpatient cataract surgery.

Material and methods: After a written informed consent 90 patients scheduled for outpatient cataract surgery with regional anaesthesia were included in this randomized, placebo-controlled double-blind study. Alfentanil (12.5 μg/kg), injected into the deltoid(n=30) or gluteal(n=30) muscle 15 min before the periocular block was compared with placebo(n=30). The plasma concentrations of alfentanil were analyzed with capillary gas chromatography. In addition to heart rate, blood pressure and oxygen saturation, subjective anxiety, sedation, nausea and pain were assessed with a visual analogue scale.

Results and discussion: In the deltoid group the mean alfentanil concentrations were significantly higher and the mean peak plasma concentrations were achieved more rapidly (table). Only alfentanil injected into the deltoid muscle was able to reduce the pain associated with the periocular block. A mild sedative effect was found in both the groups.

Conclusion: We conclude that sufficient pain relief for periocular block can be achieved with alfentanil injected into deltoid muscle. The deltoid alfentanil had a short duration of action and was not associated with any clinically significant side-effects.

Table: pharmacokinetic data

	D-group	G-group	p
Age(yrs)	74.4(4.5)	74.3(7.0)	n.s.
C_{max}(ng ml^{-1})	27.0(8.7)	8.7(2.5)	<0.001
T_{max} (min)	19.5(15.4)	64.5(48.0)	0.018
AUC (ng $l^{-1}min^{-1}$)	5531.1 (1914.2)	2805.5 (2153.3)	0.008
Cl (ml $min^{-1}kg^{-1}$)	2.50(0.79)	4.88(2.44)	0.020

A.146

PHARMACOKINETIC BEHAVIOUR OF TRANSDERMAL FENTANYL

Martine Van Bastelaere, Georges Rolly, Achiel Van Peer*
Department of Anaesthesiology, University of Ghent, Ghent, Belgium
*Janssen Pharmaceutica, Beerse, Belgium

This study reports the pharmacokinetic behaviour of transdermally applied fentanyl in 20 patients, out of a group of 40, who were randomly assigned to receive double-blind transdermal fentanyl (75 μg/h) or placebo.

Patients and methods: after approval by the Ethics Committee 40 ASA I or II informed patients, selected for major orthopaedic surgery, were studied. After 10 mg diazepam orally 120' before anaesthesia, the transdermal patch was applied. Anaesthesia consisted of propofol, small boli of alfentanil or sufentanil, vecuronium, N_2O/O_2 and isoflurane. After surgery if the patient complained of pain, morphine was given (2 mg I.V. in the recovery room and 5 mg I.M. on the ward). Plasma fentanyl levels were measured at regular intervals by RIA method (detection limit 0.1 ng/ml).

Results: after opening the code the 20 patients, receiving fentanyl, had the following gender distribution: 13 males, 7 females. The mean (±SD) age and weight were: 42.6(±13.9) y and 75.0 (±10.6) kg. The fentanyl plasma concentrations (ng/ml) are shown in table. The maximum observed concentration (Cmax) was 1.63(±0.53) ng/ml, at 32.4 (±16.1) h after application of the patch. The mean fentanyl concentration during the plateau phase was 1.31 (±0.40) ng/ml. The area under the curve was: AUC_{0-96h} 91.3(±32.8) ng.h/ml and $AUC_{0-\infty}$ 100(±37) ng.h/ml. The elimination half-life of fentanyl after removal of the patch was 16.9(±4.8) h and the elimination rate constant 0.045 (±0.015) 1/h. The clearance was 1023 (±380) ml/min.

Discussion: the attainment of useful fentanyl concentrations after transdermal application is rather slow, but after 12 h, the concentrations were fairly stable, but with wide inter-individual variations (0.84-2.95 ng/ml). The elimination half-life of transdermal fentanyl is almost 4 times larger than after I.V. administration.

Hours	Mean	SD
4	0.24 ±	0.19
8	0.60 ±	0.31
12	1.03 ±	0.44
24	1.31 ±	0.44
36	1.39 ±	0.61
48	1.33 ±	0.50
60	1.05 ±	0.52
72	0.86 ±	0.44
78	0.74 ±	0.37
84	0.53 ±	0.28
96	0.35 ±	0.26

A.147

SUFENTANIL FIRST-PASS PULMONARY UPTAKE AT THREE DIFFERENT STEADY STATE CONCENTRATIONS OF THE DRUG

Fred Boer, Frank Engbers, Toine Burm, James Bovill, Adrie Hak.

Department of Anaesthesiology, University Hospital Leiden, Leiden, The Netherlands.

Background and goal of the study. Sufentanil undergoes significant first-pass pulmonary uptake in spontaneously breathing patients[1]. Pulmonary uptake could be affected by saturation of binding in the lungs. We have investigated the effect of increasing steady state background concentrations of sufentanil on the pulmonary uptake of the drug.

Materials and methods. Ten patients scheduled for elective coronary artery surgery were studied. Patients had good left ventricular and pulmonary function. Anaesthesia was given with a computer controlled, pharmacokinetic model based infusion of sufentanil. Predicted plasma concentration for intubation of the trachea was 9 ng ml^{-1}, after which the predicted concentration was allowed to decrease to 4 ng ml^{-1}. Pulmonary uptake of sufentanil was studied during predicted plasma concentrations of 4, 8 and 16 ng ml^{-1}. During each study period indocyanine green 16.7 mg and sufentanil 65 μg was injected in 1 s via the atrial port of the pulmonary artery catheter. With a fraction collector arterial blood samples were collected at 1 s intervals for 60 s after drug injection. In each sample the indocyanine green and sufentanil concentrations were measured. Pulmonary retention ratio of sufentanil was calculated using a standard formula.

Results Measured background concentrations were 2.8 (0.66) (mean (SD)), 6.9 (1.2) and 15.9 (2.6) ng ml^{-1}. First-pass pulmonary retention of sufentanil was not affected by increasing background concentrations of the drug. First-pass retention for the 3 background concentrations was 67.6 (7.1)%, 64.7 (6.9)% and 59.9 (11.0)% respectively.

Conclusion. Sufentanil first-pass pulmonary retention is unaffected by increasing background concentrations of the drug. In the concentrations used there is no evidence of saturation of pulmonary binding sites for sufentanil.

References. 1. Boer F et al. Uptake of sufentanil, alfentanil and morphine in the lungs of patients about to undergo coronary artery surgery. Br J Anaesth 1992;68:370-375.

A.148

COMPUTER-CONTROLLED SYRINGE PUMP IMPROVES SAFETY OF PHARMACOKINETIC MODELS

DURANTEAU R., GUESDE R., RIOU B., DERIAZ H., VIARS P.
Dpt of Anesthesiology, CHU Pitié-Salpétrière, Paris, France.

Goal of study : Timing and volumetric accuracy are a prerequisite in computer-controlled intravenous (iv) infusion. Pharmacokinetic models have been described. They are "ideal" since few mention the reliability of all components : tubing, syringe, data link, computer. No real component is as defect-free as automated iv delivering systems should be. A program was developped to evaluate their incidence.

Materials and Methods : The equipment consisted of tubings, stop-cocks, a syringe pump, an RS 232 link, and a "driving" computer (PC), which run a C program. A mains/battery powered syringe pump was selected (Pilot C, Becton-Dickinson). Available flow rates ranged from 0.1 to 120.1 ml/h in 0.1 ml/h increments, with an additionnal 800 ml/h bolus. When driven by a computer, any data link failure halted the pump. Back-pressure was monitored. No patient was present since incidents were tested.

Results and discussion : Numerous events randomly interfered with the infusion process and added complexity to the system. Some were detected by the program : tubing occlusion, unclamped or empty syringe, line disconnection, time lag between a command and its execution, signal interference, battery discharge. Others had to be keyed in : drug identification, tubing leak. All events had to be monitored, evaluated, and appropriate actions done, without undue "crashing" of the pharmacokinetic model. The maximal infusion rate of the pump was somewhat too low to perform a rapid-sequence induction, unless the syringe was hand-actuated (secured in the pump clamp). Backlash in drive mechanisms has been studied by several authors, but was not included, unless an occlusion occured. Several programming techniques were considered for the driving computer : (1) *Artificial intelligence techniques* are accurate, but are complex, somewhat expensive, and not fast enough when run on today's "personnal computers". (2) *Fuzzy-logic techniques* are simple, require minimal modeling, but do not bring reproducible analytic solutions and sacrifice precision. (3) *Finite-state machines* are inherently accurate, but rely on a deep analysis of the hanshaking protocols chosen by pump makers. We choosed them to handle illegal states and transitions.

Conclusions : Many pumps implement simple computer protocols which suit ideal conditions, but real practice calls for fully-controllable devices, with safer protocols. Reliable finite-state machines can provide a cost-effective front-end to complement ideal pharmacokinetic models.

A.149

TARGET-CONTROLLED INTRAVENOUS SEDATION WITH PROPOFOL

Carine Mergaert, Georges Rolly and Linda Versichelen

Department of Anaesthesiology, University of Ghent, Ghent, Belgium

Patients and methods: a group of ten ASA I or II patients, who received locoregional anaesthesia for lower limb orthopaedic surgery, were included in this study. Epidural anaesthesia involving L3-L4 and L5 roots was performed with lidocaine 2 % plain. After successful sensory block each patient received intravenous sedation with propofol 1 %. A not yet marketed computer controlled infusion pump (Ohmeda), with a program developed by Dr Kenny, was used. A target bloodconcentration of 2 µg/ml of propofol was programmed on the pump for the whole procedure. Following assessments were made: ECG, noninvasive bloodpressure, SpO_2. An anaesthesia brain monitor (Datex) was used to assess the effect of sedation: SEMG (spontaneous electromyogram) of the frontal muscle and EEG (zero crossing frequency and mean integrated voltage) were continuously followed and graphically recorded. Bloodsamples were taken at fixed moments: at the start (To), after 15, 30 and 60 min., at the end of infusion and awake. The concentrations were measured by R.I.A.

Results: the mean (±SD) age and weight were: 49(±19) y and 61.3(±11.4) kg. All but 2 patients had a satisfactory sedation (Ramsay Score 2-3). After a computer controlled initial bolus dose (2.9 ± 0.5 ml), a statistically significant decrease of the SEMG value (50 U ⟶ 20-30 U) was noticed and these low values were observed during the whole procedure. ZXF and MIV remained stable. The propofol bloodconcentrations are shown in table. At each time period they were lower ($p<0.05$) than predicted. SEMG values returned to normal within ± 3 minutes after ending the infusion.

Conclusion: in the low dosage range the computer controlled infusion system overestimates real propofol bloodconcentrations but induces satisfactory sedation.

PROPOFOL BLOOD-CONCENTRATIONS
µg/ml

time	Mean	± S.D.
t_0	0	
t_{15}	1.3	± 0.68
t_{30}	1.2	± 0.32
t_{60}	1.2	± 0.22
t_{end}	0.9	± 0.37
t_{awake}	0.4	± 0.11

A.150

DETERMINATION OF A PHARMACOKINETIC MODEL FOR PROPOFOL INDUCTION OF ANAESTHESIA

Xavier Viviand, Catherine Guidon-Attali, Bruno Lacarelle, Claude Martin, Georges François.

Hôpital Nord and Hôpital La Timone -Marseille - France

Background and goal of study : the pharmacokinetic properties of propofol (P) make it particularly suitable for computer-assisted total intravenous anesthesia (CATIA). For short-term infusion, the pharmacokinetic model of Gepts (GPM) is suitable: bias of -2.2% and precision of 19.8% (1). The aim of this study was to evaluate the performance of this model during the first minutes of infusion : induction of anaesthesia.

Materials and methods : 10 patients, 6 men, 4 women (mean age: 52±14, range: 33-72 years, mean weight:61±16, range: 47-86 kg), scheduled for colonoscopy, were included after institutional approval and informed consent. A computer controlled an Ivac 560 volumetric pump. During anaesthesia, the patients spontaneously were breathing an oxygen-air mixture. The infusion scheme was 20 mg.kg-1 for 5 min, followed by 9 mg.kg-1 for 30min and finally 6 mg.kg-1 until 50th min. Venous blood samples were taken before and 4.5, 10, 20, 34 and 50 min after the beginning of infusion. Actual P concentrations were measured by HPLC. The determination of PM was made by weighted non-linear regression analysis. Bias was estimated by the Median Performance Error (MDPE) and precision by the Median Absolute Performance Error (MDAPE).

Results and discussion : at time 4.5 min, the GPM showed a significant bias (MDPE) : -94 % from zero ($p < 0.01$) and precision (MDAPE) was only 40 %. The calculated pharmacokinetic parameters are showed in the table. Compared to GPM, the volume of the central compartment V1 is dramaticaly higher (32 vs 16.9 L) but the value of K10 is not very different (0.146 vs 0.1190 min-1).

Conclusion : the GPM presented a poor performance to estimate blood concentrations of P during induction. The new pharmacokinetic parameters presented here seem more adequate but require further investigations to be validated.

References : 1- Anesth Analg, 1987,66,1256-63. 2- Anesthesiology, 75, A313, 1991

	Median	Coefficient of Variation
V1 (L)	32	24 %
K10 (min-1)	0.146	18 %
K12 (min-1)	0.045	42 %
K21(min-1)	0.008	170 %

A.151

PHARMACOKINETICS OF PROPOFOL AND ITS CONJUGATES AFTER CONTINUOUS INFUSION IN NORMAL AND RENAL FAILURE PATIENTS

N.NATHAN, J. DEBORD*, F. NARCISSE,
J.L. DUPUIS, G. LACHATRE*, P. FEISS.
Dept of Anaesthesiology, * Dept of Pharmacology,
LIMOGES FRANCE.

Propofol, 2-6 diisopropyl phenol, a short-acting hypnotic, chiefly metabolized by liver, has none effect on renal function. Its pharmacokinetics in end-stage renal failure patients is only known after bolus infusion. The aim of this study was to determine the pharmacokinetics of propofol and its conjugates after continuous infusion in end-stage renal failure patients as compared to normal

Methods : After approval of the ethical committee and informed consent of the patients, 6 end-stage renal failure patients (group A) and 5 ASA I patients (group B) were included in this study. Patients with cardiac or hepatic abnormalities were excluded. None premedication was done. Anesthesia was induced with propofol (2 $mg.kg^{-1}$ and 2.5 $mg.kg^{-1}$, group A and B respectively) and fentanyl (0 1 mg) then maintained with propofol (9 $mg.kg^{-1}$ and 10 $mg.kg^{-1}$, group A and B respectively) and bolus of 0.1 mg fentanyl when appropriate. Plasma propofol concentrations were determined at various intervals during infusion and during 24 H after its end by HPLC with electrochemical detection. Plasma concentration of propofol glucuronide and of other conjugates were measured after previous action of a Bèta-glucuronidase or acid hydrolysis. Preliminary estimates of the parameters were obtained by the peeling method. The number of exponentials was determined by inspection of experimental plots and computed curves, convergence of the minimization procedure and inspection of the normalized residuals. Pharmacokinetic results were expressed as median and range because of the large variability of results and compared with Man Withney-U-test.

Results : Patients were not different between groups as regard to age, sex, weight, lenght of anaesthesia and total dose of propofol (not shown). Pharmacokinetic parameters of plasma propofol are reported in table 1. The large variability of results was due to patient 1 and 5 who presented a smaller clairance and a longer last half-life. These two patients were not different from other patients as regard to demographic or biological data. The results in patient 1 might be explained by a longer sampling period (48 H). In patient 5, propofol infusion was reduced by a half because of a severe decrease of arterial pressure. Meanwhile the times of eyes opening to verbal command were not different between groups. Propofol glucuronide pharmacokinetics were not different between groups whereas the other conjugates accumulated in blood of renal failure patients (not shown).

Conclusion : The change of volume of distribution at steady state in end stage renal failure patients remained without clinical significance. Nevertheless because of high interpatient variability, accumulation of propofol might be observed after long time infusion as may occur in intensive care unit. The effects of the metabolites accumulation on drug-drug interaction deserves to be evaluated in such patients.

Table 1 : Pharmacokinetics of propofol. Median (range). * $p < 0.05$.

	Group A (n=6)	Group B (n=5)
T 1/2 α (min)	0.09 (0.44)	0.03 (n=1)
T 1/2 β (min)	0.89 (4.97)	1.01 (0.37)
T 1/2 γ (min)	16.81 (146.66)	11.51 (12.24)
Clairance ($l.min^{-1}$)	1.54 (1.2)	1.72 (0.91)
Vss ($l.kg^{-1}$)	18.80 (114.43)	8.7* (1.0.94)
Vz ($l.kg^{-1}$)	38.58 (177.45)	20.24 (26.32)
Waking concentration ($mg.l^{-1}$)	1.04 (1.66)	1.19 (0.79)

A.152

PROPOFOL (2,6 DIISOPROPYLPHENOL) AS AN ANTIOXIDANT IN-VITRO: A DOSE RESPONSE STUDY

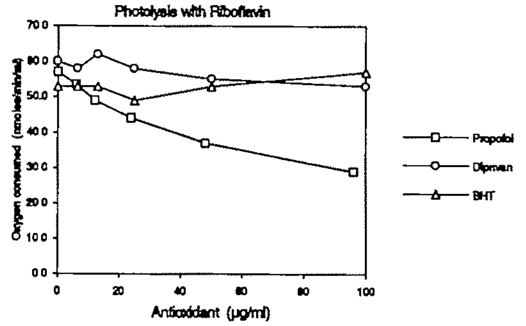
Sean Bennett, Vivienne Nelson and Terence Green
Department of Cardiothoracic Anaesthesia and Surgery,
University of Umeå, Umeå, Sweden.

Introduction: Recent work suggests propofol may have a role as an antioxidant in-vitro[1]. Also, propofol, in rat liver tissue in sufficient concentration to cause anaesthesia, has been shown to inhibit lipid peroxidation initiated by a Fenton-type free radical generating system[2]. The aim of this study was to determine the ability of propofol, at different concentrations, to inhibit organo-radicals. Diprivan (commercial propofol in intralipid) and butylated hydroxytoluene (BHT- a free radical scavenger, chemically similar to propofol) were controls.

Method: Riboflavin in EDTA/phosphate buffer was chosen as the free radical generating system as it is known to produce superoxide and organo-radicals when exposed to ultraviolet (UV) light. This system was placed in the reaction chamber of an oxygen analyzer, with a Clark electrode to measure the O_2 tension in solution. Serial dilutions of; propofol, diprivan/intralipid or BHT were then added to the chamber. The reaction chamber was illuminated with UV and the observed fall in O_2 tension was drawn on a chart recorder indicating free radical generation. The experiment was repeated with the addition superoxide dismutase (SOD).

Results: A clear dose/response curve for propofol demonstrated its ability to reduce O_2 uptake (Fig). This was not seen with diprivan or BHT. The addition of SOD allows the organo-radical component to be seen.

Discussion: The effect on O_2 uptake seen with propofol, especially in the presence of SOD which eliminates the superoxide component of O_2 uptake, supports the view that propofol's antioxidant properties are directed towards the organo-radicals rather than superoxide and hydroxyl radicals. Whether this occurs and/or its significance at clinical doses has yet to be determined.



Reference: 1. Murphy PG et al: The antioxidant effect of propofol (2,6diisopropylphenol) Br J Anaes 1992; 68,613-18. 2. Murphy PG et al:Effect of anaesthetic doses of propofol on liver cell membrane lipid peroxidation in the rat. Br J Anaes 1992; 68, 439P.

A.153

PROPOFOL ANAESTHESIA WITH SPONTANEOUS BREATHING FOR EXTRA-CORPOREAL SHOCK WAVE LITHOTRIPSY

Thomas Pasch, Tamara Hawelski

Institute of Anaesthesiology,
University Hospital, Zurich, Switzerland

Background and study aims. Initial claims of "anaesthesia-free" lithotripsy with the 2nd generation HM3 Dornier machine resulted in prolongation of procedures, and often incomplete disintegration of stones. On the other hand, since conventional general or regional anaesthesia appeared exaggerated, we introduced a technique based on an analgesic-supplemented propofol infusion, that preserved spontaneous breathing. This clinical study was aimed at assessing the practicability, ease of use, and safety of this technique during ESWL.

Material and methods. The study involved 99 patients. After premedication with pethidine (1 mg/kg i.m.) a transcutaneous PCO_2 ($PtcCO_2$) electrode (Roche) was applied to the skin of the upper thorax. After stabilization an arterial blood gas analysis was performed and the patient positioned. Further parameters monitored included ECG, oscillometric blood pressure (BP), and pulse oximetry (Oxyshuttle, Sensormedics). During localization of the stones, patients received either 20 µg fentanyl (n = 48) or 0.2 mg alfentanil (n= 51) and 4 l O_2/min were administered via a nasal tube. Anaesthesia was then induced by infusion of propofol (0.4-2.5 g/h). During the procedure, the maintenance infusion rate of propofol, supplements of analgesics and nasal O_2 flow were adjusted to meet individual needs.

Results. Onset of and recovery from, anaesthesia were rapid. There was a close linear correlation between $PaCO_2$ and $PtcCO_2$ (r=0.923). Arterial O_2 saturation (SpO_2) was stable while mean nasal O_2 flow had to be increased to 5.3±1.5 l/min. $PtcCO_2$ was 4.9±0,6 kPa before induction and increased to 6.3±0.8 kPa after 30 min. In all patients it was necessary to support the jaw (chin-lift) to keep the upper airways open. Mean BP decreased by 10-20 %, and the heart rate by 3-8 % during propofol anaesthesia. Acceptance by patients and urologists was excellent.

Conclusion. Continuous infusion of propofol is a safe and easily feasible anaesthesia technique for mildly to moderately-painful procedures. The degree of hypoventilation is clinically acceptable and oxygenation is preserved if the airways are kept open and O_2 is supplemented.

A.154

Quality of Induction: A Clinical Comparison of Etomidat-Lipuro^R and Hypnomidate^R

Wiebalck A[*], Vanacker B, Van Aken H, Sermeus L, Bouillon R[**], Amery A[***]
Department of Anesthesiology, University Hospitals, Katholieke Universiteit Leuven, Belgium

Goal: The purpose of this study was to compare etomidate in a lipid emulsion (Etomidat-Lipuro^R; Braun, Melsungen) and etomidate in propylene glycol (Hypnomidate^R; Janssen Pharmaceutica) in 110 patients in terms of anesthetic induction characteristics with special references to injection side effects, hemodynamic changes and the quality of induction.

Materials and Methods: In the first part of it, 110 patients were assigned at random to two groups in which induction of anesthesia was performed either with Etomidat-Lipuro^R or Hypnomidate^R. Anesthesia was started by iv injection of 25 µg/kg Alfentanil (Rapifen^R, Janssen Pharmaceutica). One minute later, the hypnoticum was injected in a well running intravenous line (18 G cannula). This cannula was used only for the hypnoticum and removed 15 minutes later. During injection the patients were asked to inform the anesthesiologist spontaneously and on request about the sensations at the injection place. The time from the beginning of anesthesia until the disappearance of the eyelash reflex was measured. Myocloni were documented. The patients were ventilated and vecuronium was administered to allow good intubation conditions 2 - 3 minutes later. For the first 10 minutes, blood pressure and heart rate were measured every minute. Postoperatively it was always the same investigator who made the rounds once a day and looked after the injection sites. Signs of pain, redness, swelling, induration, thrombophlebitis or thrombosis were noted.

Results and Discussion: The loss of the eyelash reflex was 42,9±8,7 s versus 42,2±11,0 s after the administration of Etomidat-Lipuro^R and Hypnomidate^R.respectively. Myocloni occurred in almost 50%, most times slightly, evenly distributed over both groups. The hemodynamic changes were minimal in both groups. After administration of Alfentanil^R, local side effects of the hypnotics were scarce with a tendency to being even weaker and more seldom in Etomidat-Lipuro^R group (3/55 versus 8/55). The postoperative vein reactions were generally mild and occurred in 17 out of 55 patients after Etomidat-Lipuro^R and in 15 out of 55 patients after Hypnomidate^R. In most cases these signs were no longer present on the second day after the procedure.

Conclusion: Alfentanil reduces the injection pain of etomidate induction agents. Local side effects are minimal after the administration of both products.

---

[*] Institut für Anästhesiologie und Operative Intensivmedizin Mannheim, Universität Heidelberg, Germany

[**] Department of Endocrinology, KU Leuven, Belgium

[***] Department of Cardiology KU Leuven, Belgium

A.155

MIDAZOLAM PREMEDICATION: A FORENSIC APPROACH TO PHARMACOKINETICS AND AMNESIA

Motsch J, Baller S, Bach A, Aderjan R*, Martin E

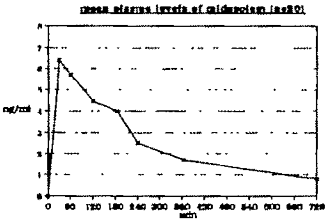
Dept. of Anesthesia, * Dept. of Forensic Medicine
University of Heidelberg, Germany

Background: Midazolam is used frequently for premedication because of its amnesic and anxiolytic effects. Benzodiazepine abuse and intoxication are frequent, and midazolam's amnesic properties are of great interest in forensic medicine. Therefore, we studied first whether the intake time and intake dose of oral midazolam can be determined by measuring the plasma level of midazolam and its 1-hydroxy-metabolite and second, whether anterograde amnesia after midazolam intake is dose dependent.

Material and methods: After institutional approval 20 patients scheduled for elective surgery were randomly allocated to receive either midazolam 7.5 mg or 15 mg for per os premedication. Blood samples were drawn at 0, 30, 60, 120, 180, 240, 360 and 720 minutes after midazolam intake. For assessment of amnesia a modified picture test was used. Plasma levels of midazolam and 1-hydroxy-midazolam were measured by gaschromatography (C. Erba Instr. GL6000 with ^{63}NiECD and a HP 3396 series II integrator).

Results and discussion: The expected metabolite 1-hydroxy-midazolam was not traceable using gaschromatography with a sensitivity limit of 5ng/ml. Maximum plasma levels of 6.4 ± 4.6 ng/ml midazolam (mean ± SD) were found at 30 minutes after intake (sensitivity limit of 1ng/ml). Unrelated to the intake dose plasma levels showed a striking variability. No patient showed anterograde amnesia in the picture test. No correlation between intake dose and test result could be demonstrated. Higher plasma levels of midazolam and 1-hydroxy-midazolam as reported by others could not be confirmed in this study.

Conclusion: Premedication with midazolam p.o. does not lead to anterograde amnesia. Analysis of the plasma level of midazolam and metabolites does not allow the extrapolation to the time of intake or the minimal oral dose taken due to the variability in metabolism.



References: Koopmans R, et al: The influence of dosage time of midazolam on its pharmacokinetics and effects in humans. Clin-Pharmacol-Ther. 1991 Jul; 50(1): 16-24. Seifert D, et al: Midazolam - a forensic problem drug. Blutalkohol 1990 Sep; 27(5): 326-31. Garzone PD, et al: Pharmacokinetics of the newer benzodiazepines. Clin-Pharmacokinet. 1989 Jun; 16(6): 337-64

A.156

DOSE DEPENDENT EFFECTS OF ORAL MEDICATION WITH MIDAZOLAM

Peter Biro, Eli Alon, Gabriele Weidmann, Sabine Pietzsch

Department of Anaesthesiology, University Hospital,
Zurich, Switzerland

Introduction: The aim of the study was to examine the psychological effects, well-being and side-effects after various doses of oral midazolam medication.

Methods: The study protocol was approved by the Ethical Committee of the University Hospital of Zurich. After informed consent was obtained, 80 adult patients in the ASA physical status I and II were randomly assigned to one of five different medication groups: 3.75 mg, 7.5 mg, 11.25 mg, 15 mg midazolam, placebo. The medication was given in a double-blind fashion 60 min before induction of general anaesthesia for various surgical procedures. At 3 definite stages (before medication, 30 and 60 min after medication), blood pressure, heart rate, transcutaneous O_2-saturation and respiratory rate were measured. Sedation and well-being were graded according to a 5-point scale, subjective fear level by visual analogue scale, concentration by standard psychometric tests. Anterograde and retrograde amnesia were measured by auditive and optic tests. Finally, patients were asked whether in case of future surgery they would prefer the same or a different medication.

Results: Demographic data were similar in all groups. There was no significant difference in respiratory rate, O_2-saturation, blood pressure or heart rate. Alertness declined slightly after 30 min in all groups; this decline was accentuated after 60 min in the groups treated with 7.5 and more mg midazolam. Decline in concentration ability was analogue to the trend in alertness. During the entire measuring period anxiolyse was in all midazolam groups not different from placebo. All midazolam groups showed a significant dose dependent amnesia compared with placebo. Subjective well-being scores showed no differences between the groups. All groups indicated a wish for the same medication in the future. Only few side-effects were seen following doses of 7.5 mg and higher, and included ptosis, strabismus, speech disorders, disorientation, and vertigo.

Conclusions: Midazolam administered orally prior to surgical procedures showed a marked inter individual variability. Sedation, decline of concentration-ability and amnesia were dose dependent and were evaluated by the patients as acceptable. Anxiolyse was not significantly different from placebo. The dose of 7.5 mg midazolam showed the best relation between desirable and undesirable effects. Adequate attention given to the patient by the anaesthesiologist prior to surgery seemed to be as important and beneficial as the oral medication.

A.157

FLUMAZENIL FACILITATES INTRAOPERATIVE AROUSAL IN SCOLIOSIS SURGERY.

Zbigniew Jerry Koscielniak-Nielsen, Jens Schierbeck,
Hanne Lisbeth Stens Pedersen, Grazyna Perko.

Department of Anaesthesia, Rigshospitalet, University
of Copenhagen, Denmark.

Background and goal of study: Early warning of spinal cord damage during scoliosis surgery is desirable to avoid permanent neurological deficit. Therefore, patients are awakened intraoperatively and instructed to move both feet on command (wake-up test) [1]. Flumazenil speeds up recovery from anaesthesia. It does not affect analgesia, which makes it suitable for arousal during extensive spinal surgery. The potential disadvantage of flumazenil is the antagonism of amnestic and anxiolytic action of benzodiazepines. This study was designed to compare speed and quality of intra-, and postoperative arousal with or without flumazenil during midazolam, fentanyl, N_2O/O_2, atracurium anaesthesia. Recovery and amnesia were also assessed.

Materials and methods: 24 adolescents with scoliosis, undergoing extensive posterior fusion of thoraco-lumbal spine, completed this randomized, double-blind, placebo controlled study. At the surgeons request the absence of neuromuscular block was ensured. N_2O was disconnected, flumazenil or 0.9% NaCl were injected in refracted doses. Patient was repeteadly instructed to move hands and feet. After the operation instructions were repeated, and the patient was requested to give full name and the date of birth.

Results and discussion: Intraoperative motor response times (median ± range) were 2.5 min (1.0-5.2) after flumazenil and 8.0 min (1.7-28.5) after placebo, (P=0.02). Five patients in the placebo group did not wake up within 10 min and received naloxone. The quality of arousal was similar in both groups. Two youngest patients (one in each group) woke up violently and needed physical restrain to avoid injury. Postoperative motor response times were 12.0 min (5-42) in the flumazenil group and 15.2 min (4-40) in the placebo group (NS). Recovery times were 27.5 min (7-415) after flumazenil and 25.0 min (8-160) after placebo (NS). Two patients (one in each group) recalled intraoperative test but had no unpleasant memories.

Conclusions: Flumazenil facilitates the intraoperative arousal during scoliosis surgery under midazolam, fentanyl, atracurium, N_2O/O_2 anaesthesia. It helps to avoid reversal of analgesia. It does not facilitate postoperative motor testing, recovery, nor does it affect recall of the intraoperative events.

Reference: Vauzelle C, et al. Functional monitoring of the spinal cord activity during spinal cord surgery. Clin Orthop 1973; 93: 173-178.

A.158

USE OF THORACIC EPIDURAL BLOCK FOR PERIOPERATIVE ANALGESIA IN CHILDREN

A H Entress, S P S Cheema

Killingbeck Hospital, York Road,
Leeds LS14 6UQ, Yorkshire, England

Although lumbar and caudal epidural analgesia is well recognised in children, there has been relatively little written about the feasibility of thoracic epidural block in infants and children mainly due to worries concerning the technical feasibility of providing such a service. Here we would like to present 11 cases of thoracic epidural block in infants and children weighing from 6 - 21kg using 0.25% Bupivicaine.

The epidural space was identified using loss of resistance at T5/6 with a 19 gauge Tuohy needle with either midline or paramedian approach and a catheter inserted for maintenance of analgesia post operatively. The initial dose of Bupivicaine was 0.3ml per kg with an infusion rate of 0.1 - 0.2ml per kg per hour post operatively.

No difficulties were experienced in inserting any of the thoracic epidurals and there was total cardiovascular stability in all cases. All cases were extubated in theatre and quality of analgesia was judged by medical and nursing staff to be excellent in all cases in the post operative period.

It was felt to be especially beneficial in cases of coarctation and due to the lack of post operative hypertension often seen in these cases, we see no reason why this technique should not be employed routinely in experienced hands to provide perioperative analgesia in all suitable cases. We are currently further evaluating the technique using thermal imaging to evaluate the extent of the block.

Results

Age (Mths)	Weight (Kg)	Operation
34	12	Coarctation
61	15	Coarctation
41	12	Empyema
63	20	Coarctation
20	12	Central Shunt
8	6	Central Shunt
62	18	Removal of pacemaker
24	12	Division of vascular ring
18	12	Coarctation
19	8	Lobectomy
8 yrs	21	Lobectomy

A.159

BLENDED ANAESTHESIA IN MAJOR PAEDIATRIC SURGERY - TOP-UP VS CONTINUOUS EPIDURAL INFUSION

G Savoia, F Lucke*, G Scermino *, B Sparacia, A Sansone

Department of Anaesthesia and Intensive Care, Palermo and Napoli* Medical Schools, Italy

Background and goal of study: Blended anaesthetic techniques include general anaesthesia for induction, maintenance of hypnosis, muscle relaxation, and loco-regional anaesthesia for analgesia and neurovegetative reflex supression. The aim was to compare two blended anaesthetic techniques using either continuous or intermittent epidural administration of bupivacaine in paediatric patients undergoing major thoraco-abdominal surgery.

Materials and methods: 40 children (3-12 years) were allocated to two groups. Group A received a continuous epidural infusion of bupivacaine 0.25% at 0.2 ml/kg/h after a bolus dose of 0.3 ml/kg during surgery follwed postoperatively by an infusion of bupivacaine 0.125% at 0.2 ml/kg/h combined with buprenorphine at 6 mcg/kg/24h. Group B received the same induction dose of buipivacaine followed intraoperatively by bolus doses of 0.2 ml/kg as needed. Postoperatively, children in group B received buprenorphine 2 mcs/kg as needed. Both groups had the same premedication (buprenorphine 3 mcg/kg + atropine 10 mcg/kg), induction (propofol 3 mg/kg), maintenance of anaesthesia (propofol 6 mg/kg/h) and muscle relaxation (atracurium 500 mcg/kg/h). Intraoperative haemodynamic instability (mean blood pressure and/or heart rate differing more than 20% from awake), insufficient depth of anaesthesia, postoperative desaturation ($SpO2<90\%$), cooperation during postoperative physiotherapy and VAS integrated score (0-10 hourly VAS score x 24h), and words more frequently used, chosen from a paediatric short form questionary (1) were recorded. The Chi-square and T-tests were used for the statistical analyses. A $p\text{-value}<0.05$ was considered significant.

Results: The main advantages of the continuous epidural technique (group A) were better haemodynamic stability ($p<0.05$), fewer children with insufficient anaesthetic depth ($p<0.05$), better cooperation during postoperative physiotherapy ($p<0.05$) and less pain ($p<0.05$).

Conclusion: Blended anaesthesia with propofol, atracurium and continuous infusion of bupivacaine at 0.25% and buprenorphine is highly recommended for the perioperative anaesthetic management of children undergoing major surgery.

Reference: (1) Savoia G, et al: Pain measure in pediatric age: procedural and linguistic aspects. Algos 1992; 9: 22-9.

A.160

CLONIDINE IN PAEDIATRIC CAUDAL ANAESTHESIA

Samir Jamali, Sylvaine Monin, Christian Begon,
Anne-Marie Dubousset, Claude Ecoffey

Département d'Anesthésie - Réanimation, Université Paris-Sud, Hôpital de Bicêtre, 94275 - Le Kremlin-Bicêtre, FRANCE

Background and goal of the study : Caudal anaesthesia was a reliable, widely used and safe technique in children. Clonidine, epidurally administered , was found to increase moderately the duration of postoperative analgesia in adults (1), it was never studied in children to our knowledge.
Material and methods : After obtaining approval of the ethics committee and a written informed consent , 22 children aged 1-7 yrs were randomized in a double-blind manner in 2 groups. After induction with halothane or thiopentone, they were all intubated with or without muscle relaxants, and a caudal anaesthesia was performed with 1ml/kg of 0.25 % bupivacaine (maximum 20 ml). Epinephrine 1/200 000 was added in group EG, or 1 µg/kg of clonidine in group CG. Anaesthesia was maintained with halothane or isoflurane only, no opioids were injected. After extubation, vital signs and haemodynamic parameters (systolic arterial pressure SAP, heart rate HR, respiratory rate RR, SpO2) were monitored every 5 min for 3 hours, then every hour for 24 hours (SAP, HR). The analgesic effect was evaluated every hour with the Broadman's (2) "objective pain-discomfort scale" (BS) until the first administration of an analgesic, which was based on pain signs, or complaint of pain in elder children. The number of analgesic administrations during the first 24 hours (AA) was recorded. Data was evaluated for statistical analysis using ANOVA tests. A Chi-square was used to compare AA and a Mann-Whitney test for BS.
Results and discussion : The two groups were identical for age (48 ± 24 vs 43 ± 23 months) (mean ± SD, respectively in group EG and group CG), weight (16.6 ± 4.7 vs 14.9 ± 3.9 kg), duration of the surgery (58 ± 48 vs 53 ± 36 min), SAP (95 ± 8 vs 98 ± 6 mmHg), and HR (115 ± 23 vs 114 ± 23 bpm). No difference was found between groups in the minimum RR (26 ± 5 vs 22 ± 3 /min with minimum values of 19 vs 17), or minimum SpO2 (97 ± 1 vs 97 ± 1 with minimum values of 95 vs 94). SAP was significantly lower in CG all over the 2 first hours after the caudal anaesthesia ($p < 0.05$), with no clinically difference (maximal mean drop was 6.5 % in CG after one hour). No bradycardia was recorded. The duration of analgesia was longer in CG (table). The maximal BS at the moment of the first analgesic administration was higher in EG (3.4 ± 1.4 vs 2.0 ± 1.2, $p < 0.05$). AA was higher in EG (2 ± 1 vs 1 ± 1, $p < 0.01$).
Conclusion : We conclude that the addition of 1 µg/kg of clonidine to the caudal anaesthesia in children is an efficacious method for the prolongation of postoperative analgesia. However, more investigation is recommended for evaluation of the side effects.

References :

1) Bonnet F et al.: Anesthesiology 1990; 72: 423-427
2) Broadman LM et al.: Anesthesiology 1987; 67: 399-402.

Table : Duration of analgesia
(mean ± SD, range, *p < 0.01)

Epinephrine group	286 ± 166 min	105 min - 720 min
Clonidine group	1009 ± 566 min *	130 min - 24 h

A.161

PROPOFOL FOR TRACHEAL INTUBATION IN PAEDIATRIC OUTPATIENT ANAESTHESIA

By : AMR MAHMOUD MONTASSER, M.D., F.R.C. Anaes. (England).
Chairman of the Anaesthesia Department, Research Institute of Ophthalmology, Giza, Egypt, Medical Director of Shaalan Surgicenter, Giza, Egypt

Background & Goal of study : Tracheal intubation is indicated in many paediatric outpatient surgical procedures. It can be achieved by deep inhalational anaesthesia or an I.V. anaesthetic and a muscle relaxant; succinylcholine being the most widely used despite its long list of side effects[1]. Propofol has been shown to be a safe induction agent in children[2], propofol also depresses the pharyngeal & laryngeal reflexes more effectively than thiopentone[3]. So, the goal of our study was to see whether propofol could be used without a muscle relaxant to facilitate tracheal intubation in children.

Patients & Methods : After ethical committee approval, 82 children admitted for outpatient Dental & ENT surgeries were randomly allocated to one of two groups. Anaesthesia was induced by N2O:O2 and halothane (0.5 - 1.5%) . Group I received thiopentone (3mg.Kg^{-1}) followed by suxamethonim (1mg.kg-1). Group II received propofol (2mg.kg-1). Intubation was carried out after 45 seconds of assisted ventilation by the same blinded experienced anaesthesiologist. He recorded the conditions for laryngoscopy (as easy or difficult) & for intubation (as : 2 = easy without coughing, 1= easy with mild coughing, 0 = followed by severe coughing or impossible). The data were presented as mean ± standard error & analysed using the student's t test or Chi square analysis as appropriate.

Results & Discussion : The two groups were well matched (age = 5.9 ± 0.4 & 5.7 ± 0.4, weight = 21.9 ± 1.4 & 22 ± 1 1kg, M/F = 27/13 & 29/13). There was no statistical difference between the two groups as regards the conditions for laryngoscopy or intubation.

Conditions for	Laryngoscopy		Intubation		
	Easy	Difficult	0	1	2
Group I	39	1	1	7	32
Group II	42	0	3	9	30
	$X^2 = 1.06$	$p = 0.3$	$X^2 = 1.07$		$p = 0.53$

So, we have found that tracheal intubation was clinically acceptable in children in about 95% of the cases using either propofol alone or thiopentone & suxamethonium.

Conclusion : We conclude that propofol following a light inhalational induction is effective for tracheal intubation in children without the use of muscle relaxants.

References : (1) Fragen R et al. Is there an Ideal Outpatient Muscle Relaxant. Problems in Anesthesia 1988, 2 : P.71. (2) Hannallah R et al. Propofol : Effective Dose and Induction Characteristics in Unpremeditated Children. ANESTHESIOLOGY 1991; 74 : 217 - 219. (3) Mckeating et al. The effects of thiopentone and propofol on upper airway integrity. Anaesthesia 1988; 43:638 - 40.

A.162

VENTILATION WITH HALOTHANE IS LESS AFFECTED IN CHILDREN WITH LARYNGEAL MASK AIRWAY THAN WITH ENDOTRACHEAL TUBE

Jean REIGNIER, Mondher BEN AMEUR, Claude ECOFFEY

Département d'Anesthésie-Réanimation, Hôpital de Bicêtre, Université Paris - Sud, 94275 - Le Kremlin Bicêtre, FRANCE

Background and goal of the study: Because of respiratory depression, with a great inspiratory rib cage paradox, spontaneous ventilation with halothane anaesthesia should be avoided in children with endotracheal tube (1, 2). Endotracheal tubes have a much higher airflow resistance than laryngeal masks airway (3). Therefore, we sought to determine whether the lesser additional respiratory work induced by laryngeal mask airway authorizes or not spontaneous ventilation with halothane anaesthesia in children.

Materials and methods: We studied two groups of 6 to 24 months-old children free of cardiorespiratory and neurological disorders. They all were undergoing elective minor surgery: group 1 (n = 9) with laryngeal mask airway, group 2 (n = 10) with endotracheal tube. They received randomized administration of two halothane concentration: 1 and 1.5 Minimum Alveolar Concentration (MAC). We measured tidal volume (Vt), respiratory rate (RR), minute ventilation (VE, pneumotachygraph), CO2 end-tidal pressure (PetCO2) and we assessed inspiratory rib cage paradox by indices of amplitude (AI) and phase delay (DI). All the results are expressed as mean ± SD. Statistical analysis was made by a two ways ANOVA followed by Newman - Keuls test (p < 0.05 was considered significant).

Results and discussion: Age and weight were similar in both groups. All the respiratory parameters are summarized in the table :

	Vt/kg (ml/kg)		RR (/min)		VE/kg (ml/min/kg)	
	1	1.5	1	1.5	1	1.5
group1	9.4	7.1	41	43	385	301
	± 4.7	± 2.3*	± 6	± 7	± 179	±107*
group2	5.5	4.6	47	52	251	223
	± 1°	±1.2*°	± 11	± 13	± 36	± 29*

	PetCO2 (mmHg)		AI (%)		DI (%)	
	1	1.5	1	1.5	1	1.5
group1	41	46	23	32	18	15
	± 9	± 9	± 38	± 51	± 11	± 11
group2	40	44	59	106	40	49
	± 6	± 6	± 57	±86*°	±19*°	± 20*°

* p<0,05 vs MAC 1 , °p<0,05 vs group 1.

In accordance with literature, we found that minute-ventilation was depressed with halothane in a dose-dependant way (1). Tidal volume was less depressed with laryngeal mask airway than with endotracheal tube. The rib cage paradox indices were significantly (p < 0.001 for DI at 1.5 MAC) less altered with laryngeal mask airway than with endotracheal tube.

Conclusion: Spontaneous ventilation could be used with a laryngeal mask airway in 6 to 24 months-old children with halothane anaesthesia.

References:

1) Murat I et al. Br. J. Anaesth. 1985 ; 57: 569-572
2) Ben Ameur et al. Am Rev Resp Dis 1992 ;145: A557
3) Bhatt et al. Anaesthesia 1992 ; 47: 343-347

A.163

NEUROMUSCULAR BLOCKADE FOLLOWING MIVACURIUM IN CHILDREN DURING N20-HALOTHANE

Gilles Orliaguet, Benoit Plaud, Sylvie Calmatte*, Claude Ecoffey

Département d'Anesthésie - Réanimation, Université Paris-Sud, Hôpital de Bicêtre, 94275 - Le Kremlin-Bicêtre, FRANCE and * Welcome Laboratories

Background and goal of the study : Mivacurium is the latest, non depolarising neuromuscular blocking to become available in man. Pediatric data so far is limited (1). The aim of this study was to determine onset, duration of action and recovery characteristics in the child during N2O-halothane anesthesia.

Material and methods : Ten ASA status I-II children, aged between 1.3 and 6.8 years were studied following institutional approval and written informed consent from parents. All patients were scheduled for surgery requiring the use of neuromuscular blocking agents. Anaesthesia was induced with N2O (50 %) in O2 and halothane. The trachea was intubated and anaesthesia was maintained with an end-tidal halothane concentration of 1 MAC (age adjusted). Ventilation was controlled to maintain an end-tidal CO2 between 30 and 36 mmHg. Monitoring included ECG, non invasive blood pressure, end-tidal CO2, end-tidal halothane and Sp02. The ulnar nerve was stimulated supramaximally via skin electrodes at the wrist using a TOF stimulation every 10 sec. The force of contraction of the adductor pollicis was measured using a paediatric force transducer. After a stable recording had been achieved for 5 minutes, 0.2 mg.kg-1 of mivacurium was injected iv over 15 sec and flushed immediately. Following maximal blockade the stimulation rate was reduced to once every 20 sec. Onset time (time from injection to maximal blockade), clinical duration (time from injection to 25 % recovery), recovery index (time from 25 % recovery to 75 % recovery), total duration (time from injection to 90 % recovery) and the time from injection until T4 recovered to 80 % of T1 were measured. All results are expressed as mean ± SD. Systolic blood pressure and heart rate prior to injection and five minutes after were compared using ANOVA following by appropriate post-hoc test (p < 0.05 was considered statistically significant).

Results and discussion : Results are displayed on the table. All patients showed 100% block with the dose used. Systolic blood pressure was 93 ± 4 mmHg and 87 ± 3 mmHg respectively before and 5 min following injection of mivacurium, similarly heart rate was 99 ± 5 and 101 ± 5 bpm.

Table	mean ± SD	Range
Onset (sec)	68.5 ± 6.6	50 -120
Clinical duration (min)	12.5 ± 1.4	4 - 21.5
Recovery index (min)	3.4 ± 1.6	1.2 - 6
Total duration (min)	19.2 ± 5.9	11.3 - 31.9
Time to T4/T1 = 0.8 (min)	19.1 ± 6.4	10 - 28.7

Previous work has demonstrated the ED 95 of this drug to be 95µg/kg^{-1} in 2-12 years old children (2). As it is usually considered that the intubating dose is twice the ED 95, we therefore used 0.2 mg.kg^{-1}. Following this dose, the onset time (68 sec) is more rapid than estimated equipotent doses of atracurium in children during N2O-halothane anesthesia (3). The duration and recovery index are shorter.

Conclusion : At the dose of 0.2 mg.kg^{-1} in children mivacurium is a neuromuscular blocker which produces 100% blockade with a short onset time and a short duration of action.

References : 1) Anesth Analg 1989; 68: 116-121
2) Anesthesiology 1989; 70: 237-242
3) Anesthesiology 1983; 59: 459-462

A.164

RELATIONSHIP BETWEEN ARTERIAL PCO2 (PaCO2) AND END TIDAL CO2 (ETCO2) RECORDED THROUGH A LARYNGEAL MASK (LMA) IN CHILDREN BREATHING SPONTANEOUSLY.

LJ VAN OBBERGH, B ZEIPPEN, G MULLER, F VEYCKEMANS.
DPT of ANAESTHESIA ,UCL MEDICAL SCHOOL , 10 av Hippocrate ,1200 BRUSSELS

This study compare the ETCO2 and the PaCO2 in 25 ASA 1or 2 children undergoing Xray examination under propofol infusion and breathing spontaneously through a LMA (Size 1: 6 cases , Size 2: 19 cases) as we already described it (1).

ETCO2 was recorded through a 20 G catheter inserted 4 cm in the LMA with a DATEX NORMOCAP infrared capnometer calibrated before each case . 50% N2O in O2 was provided through a modified Ayre T piece , the fresh gas flow was adjusted to avoid any rebreathing on the capnogram . ETCO2 was recorded when a well identified plateau was reached during at least 5 min. . Arterial blood was drawn after a single puncture of the femoral artery and PaCO2 measured with a CIBA CORNING blood gas analyser.

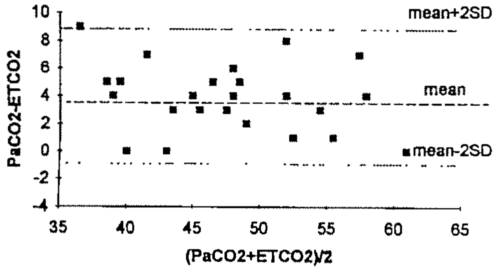
Linear regression (LR) was used to assess the correlation between the two parameters and the method described by Bland and Altman to measure their agreement (2) (Cf. fig 1)

RESULTS: (All results are expressed as MEAN ± SEM).

Age (Months):	37 ± 3.9
Weight (Kg):	19 ± 1.8
Respiratory rate (Breaths/min.)	22 ± 1.3
ETCO2 (mmHg):	45.2 ±1.2
PaCO2 (mmHg):	49.2 ± 1 3
Pa CO2-ETCO2 (mmHg):	3.8 ±0.5 SD ±3.4

LR of ETCO2 on PaCO2: PaCO2 = 10 +0.89 ETCO2 R=0.91 P=0.001

Fig 1: Agreement measure



CONCLUSIONS

Although the mean difference between the PaCO2 and the ETCO2 is near the values recorded with an endotracheal tube (3), the agreement limits seem to be greater and caution must be exercised when one is reading the ETCO2 with a LMA. The difference may be as great as 9 mmHg even in stable conditions .

(1) Anesthesiology: 77,A1177,1992.
(2) The Lancet:Feb 8 ,307-310,1986
(3) Can Anaesth Soc J 29:13, 1982.

A.165

EVALUATION OF THE EFFICACY OF FORCED-AIR WARMER (BAIR HUGGER) DURING SPINAL SURGERY IN CHILDREN

Isabelle Murat, Josée Bernière, Isabelle Constant

Dpt of Anaesthesia, Hopital Trousseau, Paris, France.

INTRODUCTION

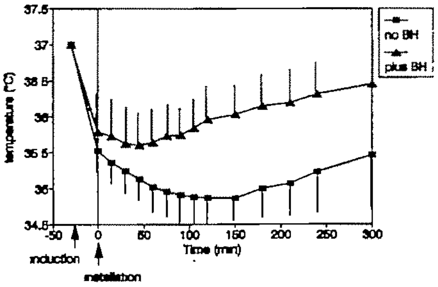
This study was undertaken to evaluate the efficacy of a forced-air warmer (Bair-Hugger) in children scheduled for surgical spinal fusion. Spinal surgery is an hemorrhagic procedure of long duration commonly associated with intraoperative hypothermia as active skin warming is difficult owing to the surgical position

METHODS

Fifty one consecutive children scheduled for posterior spinal fusion were studied. Anaesthesia was induced with propofol and pancuronium, and maintained with isoflurane and intermittent injections of pancuronium and phenoperidine. Moderate hypotension (mean arterial pressure 50-60 mmHg) was achieved with isoflurane and nitroglycerin (1-3 mcg.kg-1.min-1). Monitoring included EKG, arterial pressure, SpO2, expired gas (CO2, isoflurane) and rectal temperature. An open circuit with an heat moisture exchanger was used in all children. The study started after installation of the patient in the prone position. The study group (BH+; n=26) had the forced air warmer placed on the lower limbs, thus covering 30 to 40 % of the surface body area. In the control group (BH-; n=25), temperature was maintained with radiant heater placed near the head of the patient. Temperature of the operating room was 22-24°C. A wake-up test was performed after placement of the rods (CD material) upon request by the surgeon by discontinuing isoflurane and N2O. Temperature was continuously monitored during surgery and during the first two hours in the recovery room. Demographic data, temperature values, blood loss, time to wake-up test and extubation were compared between the two groups with the use of student's T test. P values of 0.05 or less were considered as significant. Results are mean ± SD.

RESULTS

No differences between groups were observed regarding age (BH- vs. BH+; 14.9 ±2.2 vs. 14.7 ± 1.7 years), weight 45.6 ± 8 9 vs. 47.9 ± 13.8 kg), duration of surgery (5.8 ± 2.0 vs. 4.8 ± 1.2 h), duration of induction before installation (33.4 ± 12.5 vs. 32.5 ± 16.2 min). No differences were also observed for time to obtain a positive wake-up test, time to extubation and total blood loss per vertebra. The evolution of mean rectal temperature in the two groups is indicated on the figure.



CONCLUSION

The Bair-Hugger was more effective than conventional methods to maintain body temperature during surgery despite only 30 to 40 % of body surface area was covered during surgery.

A.166

EVALUATION OF A FORCED-AIR WARMER (BAIR-HUGGER) IN MAINTAINING BODY TEMPERATURE IN INFANTS DURING CLEFT PALATE SURGERY.

I. Murat, M. Delorme, V. Piat, M.C. Dubois

Dpt of Anaesthesia, Hopital Armand Trousseau, Paris, France.

INTRODUCTION

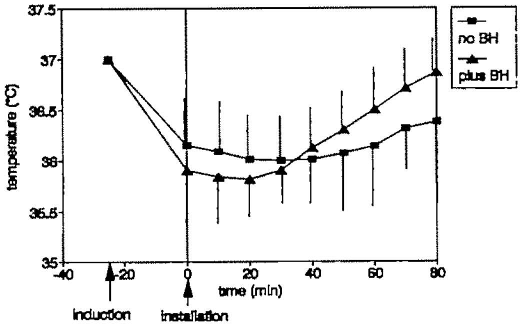
Congenital clefts of the lip and/or palate are usually repaired early in infancy for cosmetic reasons and to improve the development of the alveolar dental arch. This study was undertaken to assess the efficacy of a forced-air warmer (Bair-Hugger) in maintaining body temperature during surgery as compared to conventional means.

METHODS

Infants weighting less than 10 kg scheduled for cleft of the lip or palate repair were assigned to two groups. In the study group (BH+; n=25), the Bair-Hugger was placed on the lower part of the body after induction of anaesthesia and tracheal intubation. In the control group (BH-; n=19), body temperature was maintained with a water mattress placed under the body covered with surgical drapes. Temperature was monitored rectally every 10 min during surgery and for the first 2 hours in the recovery room. In both groups, anaesthesia was induced with halothane by face mask and maintained with isoflurane and fentanyl (2-3 mcg.kg-1). An open circuit with an heat moisture exchanger was used in all infants. Temperature of the operating room was set at 24°C in both groups. Comparisons of demographic data, temperature values, time to extubation, were done using student's t-test. $P<0.05$ was considered as significant. Results are mean ± SD.

RESULTS

The two groups were identical regarding age (BH- vs. BH+; 5.3 ± 2.6 vs. 5.1 ± 2.2 months), weight (6.5 ± 1.3 vs. 6.3 ± 1.4 kg) and duration of surgery (95 ± 26 vs. 97 ± 23 min). No differences in rectal temperatures were observed between groups during surgery (figure). Time to extubation was also identical in the 2 groups (23 ± 10.5 vs. 26.4 ± 18.7 min). No differences were observed in the recovery room while more infants in the BH- group required a radiant warmer to maintain their temperature than in the BH+ group.



CONCLUSION

Both forced-air warmer and water mattress were effective in maintaining central temperature in infants when operating room temperature is as high as 24°C.

A.167

COMPARISON OF DOBUTAMINE WITH ENOXIMONE FOLLOWING OPEN HEART SURGERY IN SMALL CHILDREN

P. Innes, E. Allsop, J.Lockie, C. Kirton, P.Booker. Department of Paediatric Anaesthesia, Royal Liverpool Children's Hospital, Liverpool, England.

Background and goal of study: Dobutamine and enoximone are often used following heart surgery, though few studies have examined their respective haemodynamic effects in children. This study aims to compare the effects of these 2 drugs in children having open heart surgery.

Materials and methods: 25 children, mean age 1.22 yrs (0.42-3.83yrs), scheduled for elective correction of either tetralogy of Fallot or atrioventricular septal defect (AVSD) were randomly allocated into one of two groups. Group 1 received dobutamine (D) (10mcg/kg/min) and phenoxybenzamine 1 mg/kg and group 2 enoximone (E) 10 mcg/kg/min following a loading dose of 0.5mg/kg. The trial drug was started 10 minutes prior to the anticipated cessation of cardiopulmonary bypass (CPB). Heart rate (HR), mean systemic and pulmonary arterial pressures (MAP & MPAP), central venous and left atrial pressures (CVP & LAP) and cardiac index (CI) by the thermodilution technique were measured at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5 and 6 hours after CPB. Systemic vascular resistence index (SVRI) and left ventricular stroke work index (LVSWI) were calculated using conventional formulae. Variables for each patient were plotted against time and area under the curve calculated giving a mean value for each variable. Statistical analysis was by the unpaired students t test.

Results and discussion: There were no significant differences between the 2 groups of patients with respect to age, operation type and aortic cross-clamp times:- D: 77.2 mins (65-85) E: 76.7 mins (65-89). 3 patients (E:2, D:1) also required adrenaline in order to be weaned from CPB. There was no significant difference between the 2 groups with respect to HR, CVP, LAP and MPAP and SVRI. D was associated with a higher MAP (D 61.7mmHg 7.9sd;E 55.8mmHg 5.6sd:$P=0.05$); a higher CI (D 2.89 L/min/m2 0.65sd;E 2.40 L/min/m2 0.38sd:$P<0.05$); and a higher LVSWI (D 12.98 J/m2 4.97sd;E 9.53 J/m2 1.97sd:$P<0.05$) indicating greater inotropic effect.

Conclusion: This study shows that enoximone can be used successfully to wean children from CPB. However, dobutamine, in combination with phenoxybenzamine, has greater inotropic and similar vasodilatory properties than enoximone in the doses used.

A.168

EXREACORPOREAL MEMBRANE OXYGENATION FOR POSTOPERATIVE CARDIAC SUPPORT IN NEWBORN INFANTS: FIRST CLINICAL DATA

A Marcassa, C Sorbara, G Stellin, D Pittarello, GP Giron

Department of Anaesthesia and Intensive Care, University of Padua, Padua, Italy

Background and goal of study: Extracorporeal membrane oxygenation (ECMO) has been used successfully to treat newborn infants with respiratory failure that is unresponsive to ventilatory and pharmacologic support. We describe our experience of the use of veno-arterial ECMO to support cardiac function in paediatric patients who have developed low cardiac output syndrome after surgical repair of congenital heart defects.

Materials and methods: From March till October 1992 we have treated 6 newborn infants (age 2-32 days, weight 2.7-3.8 kg) who required ECMO in the operating room since they could not be weaned from cardiopulmonary bypass after open cardiac operations (3 hypoplastic left heart syndromes, 1 transposition of the great arteries, 2 complex obstructive lesions of the right ventricle). We performed thoracic cannulations using a 10F cannula for the aorta and a 16F cannula for the right atrium. Pump flow was >110 ml/kg/min in all patients. The ECMO circuit consisted of a Biomedicus centrifugal pump, a SciMed membrane lung and a SciMed heat exchanger.

Results and discussion: The duration of ECMO ranged from 4 to 143 h (mean 55.6 h). 4/6 patients could be weaned from ECMO. Only 1/4 is a long-term survivor. The other three children died in the intensive care unit; two shortly after weaning from ECMO and the third after four days. Two patients could not be weaned from ECMO because of irreversible cardiac failure. Bleeding was the most frequent complication averaging 6.45 ml/kg/h. One patient had an intracranial haemorrhage. Renal insufficiency developed in two patients. No technical complications of ECMO occured.

Conclusion: ECMO is a successful procedure in treatment of neonatal respiratory failure with an overall survival rate in the order of 85%. Veno-arterial ECMO can also be used for temporary circulatory support in severe cardiac failure after cardiac surgery. Similar to previous reports which show that survival rate is correlated with the time of ECMO initiation, our results indicate that patients requiring ECMO in the operating room have a high mortality.

A.169

DIAMORPHINE/BUPIVACAINE MIXTURE VS PLAIN BUPIVACAINE: A COMPARISON OF EPIDURAL INFUSIONS IN LABOUR

CR Bailey, R Ruggier, IL Findley

Department of Anaesthetics, St Georges Hospital, London, UK

Background and goal of study: Analgesia in labour should be safe, effective and feasible. Both local anaesthetics and opioids are effective via the epidural route and the aim of this study was to compare plain bupivacaine 0.125% run at 10 ml/h with a low dose bupivacaine/diamorphine infusion run at the same rate. By using the lowest effective dose of each drug in combination we attempted to eliminate any side effects whilst providing excellent analgesia in labour.

Patients and methods: 50 healthy patients in active labour were studied following Ethics committee approval. After insertion of the epidural a loading dose of 8 ml 0.5% plain bupivacaine was given to all patients, who were then randomised to receive either plain bupivacaine 0.125% or plain bupivacaine 0.0625%/diamorphine 0.005%. Hourly Visual Analgue Pain Scores (VAPS) were obtained by Midwives and top-ups of 10 ml 0.25% bupivacaine were given if required. Assessment of motor blockade and sensory level were repeated every hour. Blood pressure, heart rate, respiratory rate and fetal heart rate were recorded every 30 min. Mode of delivery and condition of neonate were noted and a questionnaire completed by the mother on the day after delivery which included direct questioning for symptoms such as pruritus and nausea.

Results and discussion: Age, weight and height were similar in both groups. Patients in the diamorphine group had significantly more painfree hours (54 vs 32 in control group, $p<0.01$ by Chi-square) and greater satisfaction with the infusion, but there was no difference in the incidence of hypotension or instrumental delivery, number of top-ups, duration of second stage or extent of motor block. Moreover, patients in the diamorphine group had a higher incidence of pruritus (44% vs 0% in control group). Enever et al used a diamorphine/bupivacaine mixture in labour but patients received only 1.05 mg of diamorphine/h compared to 3.08 mg/h in this study and had a higher incidence of motor block but low incidence of pruritus, and results from other studies show that both diamorphine and bupivacaine produce dose-related side effects.

Conclusion: The addition of epidural diamorphine at 0.5 mg/h to a solution of 0.0625% bupivacaine produces additional opioid-related complications without reducing the side effects which occur with 0.125% bupivacaine alone.

Reference: Enever, et al: Epidural infusion of diamorphine with bupivacaine in labour. Anaesthesia 1991; 46: 169-173.

A.170

PATIENT CONTROLLED EPIDURAL ANALGESIA VS. INTERMITTENT INJECTIONS DURING LABOR USING 0.125% BUPIVACAINE AND SUFENTANIL.

J. Baudot, J.D. Vertommen, H. Van Aken.

Department of Anesthesiology, University Hospitals,
Katholieke Universiteit Leuven,
Herestraat 49 B-3000 Leuven, Belgium.

Background and goal of study: The addition of 7.5 μg sufentanil to 0.125% bupivacaine with epinephrine (1:800,000) enhances the quality of analgesia during labor without depressing the neonate when the mixture is given as intermittent 10 ml injections. (1,2). The present study was undertaken to investigate if patient controlled epidural analgesia (PCEA) using an identical anesthetic mixture provides a comparable quality of analgesia.

Materials and methods: With institutional approval and informed consent, 74 pregnant women who requested epidural analgesia for labor were included in this prospective study and randomly assigned to 2 groups of 37 women each. They received either intermittent injections given by an anesthesiologist (A), or PCEA (B). In all women analgesia was induced by epidural injection of 10 ml containing 12.5 mg bupivacaine, 12.5 μg epinephrine and 7.5 μg sufentanil. In group A analgesia was further maintained by 10 ml injections of the same mixture on request. In group B, analgesia was provided by self administration of 4ml boli of 0.125% bupivacaine with epinephrine (1:800,000) plus sufentanil 0.75μg/ml with a lock-out interval of 20 min. The quality of analgesia was assessed on a linear visual analog scale before the first epidural injection, then each hour, and during episiotomy, delivery, and suturing. Patient satisfaction was also rated on a visual analog scale, 1 hour after delivery. The duration of analgesia, the degree of motor blockade, and the total volume of anesthetic mixture were noted. The neonates were evaluated by Apgar scores. Statistical analyses were done by Student-t test and chi-squares. A P value < 0.05 indicated significance.

Results and discussion: Patient characteristics of both groups were comparable. The mean pain relief in both groups was 80% and there was no difference in pain score between the groups during episiotomy, delivery, or suturing. Motor blockade and type of delivery did not differ between the groups. Patients in group B used less anesthetic mixture, but this difference did not reach statistical significance. Although in group A the delay between request and injection was significantly longer than in group B, patient satisfaction was similar.

Conclusion: PCEA and intermittent injections using 0.125% bupivacaine and sufentanil provide a comparable quality of analgesia during labor.

References: 1. Vertommen JD, et al: The effects of the addition of sufentanil to 0.125% bupivacaine on the quality of analgesia during labor and on the incidence of instrumental deliveries. Anesthesiology 1991; 74: 809-814
2. Lemmens E, et al: Epidural sufentanil during labor: comparison of three different doses: 5, 7.5, and 10 μg. Anesthesiology1992; 77: A988.

A.171

ADEQUATE PAIN RELIEF WITH EPIDURAL ANALGESIA DURING LABOR : WHY ARE WOMEN STILL DISSATISFIED ?

Jamil Hamza, Patrick Narchi, M Elhaddoury, Dan Benhamou

Département d'Anesthésie, Université Paris Sud, Hôpital
Antoine Béclère, 92141 Clamart, France.

Background and goal of study: Inadequate pain relief with lumbar epidural analgesia (LEA) is a classical cause of parturient's dissatisfaction. However, even when this technique has been efficient, some women remain dissatisfied. The goal of this study was to define other factors associated with patient's dissatisfaction in a large obstetrical population.

Materials and methods: After institutional approval and over a 2 years period, all parturients who delivered vaginally under LEA participated to this study. All data related to LEA and the delivery period were noted. During the 3 first days postdelivery, a questionnaire aimed at understanding the reasons of dissatisfaction about LEA was given to these patients. Specific items were the following: global satisfaction, adequacy of pain relief, quotation of pain associated with epidural puncture, relationship with the anesthetist, time interval between request and epidural puncture. The first step of the study was to assess the role of the inadequacy of pain relief as a factor of dissatisfaction. The second step aimed at assessing in the subgroup of women who were adequately relieved of pain, the factors associated with their dissatisfaction. Statistics of all collected data included either unpaired Student's t-test or a Chi square test for qualitative data: $p<0.05$ was considered as statistically significant.

Results and discussion: Of the 1297 women who were included, 1058 (82%) had adequate pain relief whereas 239 (18%) had not. Global satisfaction in patients who had inadequate pain relief was significantly lower than in those with adequate pain relief. Women **adequately relieved** were thus divided into 2 groups with respect to their overall satisfaction concerning LEA: Satisfied (S) n=1034 and dissatisfied (**disS**) n=24. Demographic data, duration of labor, newborn's weight, parity, cervical dilatation at the time of puncture and the total dose of bupivacaine were comparable between both groups. Risk factors associated with patient's dissatisfaction with LEA were the following: a bad human relationship with the anesthetist performing EA, a painful epidural technique and a long delay between request and puncture (Figure).

This study confirms that inadequate pain relief remains a major cause (84.4 %) of dissatisfaction with LEA. However, a long time interval between request and puncture, a painful epidural puncture and a bad relationship between the patient and the anesthetist are to be considered as significant factors of dissatisfaction even if pain relief is adequate throughout labor.

Conclusion: Anesthetists must be aware of the importance of these factors and that pain relief is not the only goal to achieve in order to satisfy laboring women.

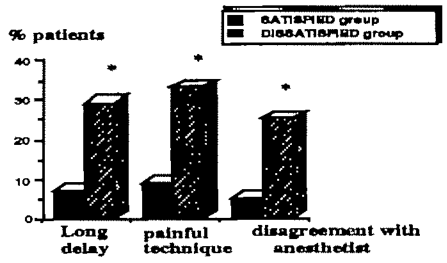


Figure 1: % patients presenting these features in the group adequately relieved (n=1058)

A.172

SPINAL ANESTHESIA FOR C SECTION : ADDITION OF PHENYLEPHRINE TO EPHEDRINE FOR PREVENTION OF MATERNAL HYPOTENSION.

Anne-Valérie Thirion, Michel Henry, Annette Cornet,
Jeanne Seebacher, Pierre Viars.
Department of Anaesthesiology, CHU Pitié-Salpêtrière, Paris, France.

Ephedrine is considered as the vasopressor of choice in obstetrical anesthesia. However, particularly for C section performed under spinal anesthesia, larges doses are needed which may lead to side effects (i.e. tachyphylaxia, tachycardia). Recently, clinical studies shown phenylephrine, an alpha agonist, to be as efficacious and safe as ephedrine (1). This study was designed to evaluate whether the addition of a small dose of phenylephrine to an ephedrine infusion could provide hemodynamic stability throughout C section performed under spinal anesthesia.

Patients and methods: Thirty patients ASA I scheduled for elective C section were studied. After 25 ml/kg of ringer lactate solution preloading over 30 minutes, spinal anesthesia was induced with 12,5 mg Bupivacaïne 0,5 % and 0,1 mg Morphine in the left lateral decubitus position. At the time of the spinal puncture, patients received a continuous I.V. infusion of phenylephrine (60 mcg) and ephedrine (7,5 mg) over a 15 minutes period. Additional ephedrine was given in 3 mg boluses if blood pressure was not stable. These patients were compared to 30 patients ASA I who underwent the same anesthetic and surgical procedure but received a continuous infusion of only ephedrine 7,5 mg over a 15 minutes period.

Results: Maternal weight, height, neonatal Apgar scores are not statistically different between the two groups. Maternal blood pressure was stable throughout the surgical procedure in both groups but more patients receiving only ephedrine required additional ephedrine (table). A significant increase in maternal heart rate (HR) was noted only in patients receiving ephedrine (ANOVA $p<0,05$). Besides post-infusion HR was higher in this group of patients.

	Additional Ephedrine		
nb of boluses	0-1	2 - 4	> 4
Ephedrine + Neo	n = 18	n = 9	n = 3
Ephedrine	n = 7	n = 12	n = 11

Conclusions: We conclude that the addition of a small dose of phenylephrine to an ephedrine infusion was easily useable and effective in preventing maternal hypotension without increasing maternal heart rate.

Reference: Acta Anesthesiol.Scand,1988,32:559-565.

A.173

HEADACHE - NEW NEEDLES AND SPINAL ANESTHESIA FOR C. SECTION

F. Thormann, M. Henry, J.P. Soler,
J. Seebacher, P. Viars
Department of Anesthesiology.
CHU Pitié-Salpêtrière. Paris. France

Background and goal of study. The highest incidence of postdural puncture headache (PDPH) occurs in obstetric patients (1). With the blunt ogival spinal needle, with side opening, we performed 300 c. section (ASA I) without any severe PDPH, like other authors (2). The aim of this study was to collect the different headache after spinal c.-section with different blunt and ogival needles.

Materials and method. 103 ASA I parturients underwent elective c.-section with the same anesthetic protocol : left uterine displacement, filling 25 ml/kg of saline and ephedrine (continuous infusion and bolus), 2) intrathecal injection of 0.1 mg of morphine and 12.5 mg of hyperbaric bupivacaine. The anesthetist was free to choice between a 1) 22 gauche Sprotte needle, 2) 24 gauche Sprotte needle, 3) 25 gauge modified Whitacre (Vygon-Portex). On postoperative days (1 to 6) a blinded anesthetic nurse evaluated each patient to determine the incidence of headache ; then the anesthetist, after patient examination, classified the headache according to three groups 1) **minor**, transitory headache (postural or not) not requiring any analgesic; 2) PDPH = postural headache always treated by recumbent position : a) **middle**, requiring simple oral analgesics, lasting 2 or 3 days, b) **severe**, incapaciting for the mother, lasting a week or more ; the only efficacious treatment is the blood-patch.

Results. We don't find any severe PDPH ; there is a tendency, to be confirmed, to a highest incidence of middle PDPH with the 22 gauge needle ; the headache are not correlated to difficult punction.

n	Needle	Gauge	Minor	Middle (a)	Severe(b)
48	Sprotte	22	5	4	0
35	Sprotte	24	5	1	0
20	Whitacre	25	2	1	0

Discussion. The lack of severe PDPH is confirmed in ASA I. PDPH decreased with blunt ogival needle ; but higher gauge is yet associated with a higher incidence of middle PDPH (well accepted by the mother).

Conclusion. We can propose spinal anesthesia with the blunt ogival needle at gravid young women who are the classical highest risk of severe PDPH.

1. Gerard et al. Semin. Anesth., 1990, 9 : 69-74
2. Cesarini M. et al. Anesthesia 1990 ; 45 : 656-658

A.174

BEST QUINCKE POINT NEEDLE FOR CAESAREAN SECTION

Gordon Lyons

St James' University Hospital,
Leeds, UK.

The incidence of post dural puncture headache is influenced by age, sex and the mode of spinal anaesthesia. Of particular importance is the size and nature of the spinal needle. A number of studies claim a reduction in the incidence of headache following spinal anaesthesia for Caesarean section if a pencil point needle is used in preference to a Quincke point. Before the case for pencil point needles can be accepted, it is necessary to establish which Quincke point needle is the best for Caesarean section. This study aimed to establish the best Quincke point spinal needle for Caesarean section.

Hospital ethics committee approved this study. 300 women scheduled for elective Caesarean section under combined spinal/epidural anaesthesia were randomised to receive their anaesthetic with a 26 gauge, a 27 gauge, and a 29 gauge needle. Established clinical procedures were followed. Observations included:
Time from gloves to intrathecal injection
Number of suspected dural punctures
CSF seen/not seen
Anaesthetist's assessment of block
Patient's assessment of block
Incidence of postoperative headache

The 29 gauge needle was associated with more failed sitings and need for epidural support than the other two needles. This was statistically significant. Five patients in the 26 gauge group required epidural blood patches, compared with one each in the other groups. This did not reach statistical significance. In conclusion, the 29 gauge needle had the most failures, and the 26 gauge needle, the most headaches. the 27 gauge needle appears to be the best Quincke point needle for Caesarean section.

A.175

NEONATAL GLYCEMIA: DOES THE MATERNAL IV FLUID REGIMEN DURING LABOR MAKE A DIFFERENCE?

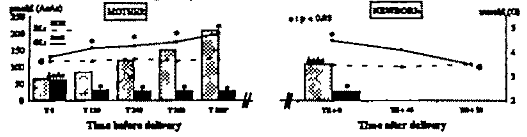
C. Menigaux, J. Hamza, P. Bougnières, Cl. Saint-maurice

Departement of Anesthesia, Inserm U342, Hospital Saint
Vincent de Paul, Paris, France

Background and goal of the study: Maternal glucose infusion during labor was recommanded to avoid maternal and fetal hypoglycemia(hypoG). However, when uncontrolled this practice may lead to neonatal hypoG(1). Therefore, we decided to prospectively compare the maternal and neonatal consequences of two maternal iv fluid regimen with or with out controlled glucose administration during vaginal delivery.

Patients and methods: 20 ASA 1 parturients with a normal singleton pregnancy entered the study in active labor (cervical dilatation < 3 cm). After a fasting duration of at least 10 hours, they were randomly allocated to receive as a continuous iv infusion either 20 ml/h of 50% dextrose (150 mg/kg/h of glucose) (group GL) or 20 ml/h of Ringer lactate (group RL). In both group, a basal iv infusion of 100 ml/h of Ringer lactate was administered with a iv bolus before epidural analgesia(EA).of 15 ml/kg. Glycemia(G), aceto-acetic acid(AcAc), lactic acid(L), free fatty acid(FFA) were measured every two hours until delivery in maternal plasma. In the newborn G, AcAc, L, FFA and insulinemia(Ins) were measured at birth, and also G at 45 and 90 min of life using dextrostix. Statistical analysis used paired and unpaired Student's t test.

Results and discussion: Weight, age, duration of labor and initial biological parameters were similar. Despite a fasting period > 10 h, no parturient had a G < 3,3 mmol/l throughout labor even in the RL group. In contrast one parturient in the GL group had a G > 6,6 mmol/l which is a risk factor for neonatal hypoG(1). However neonatal G was never < 2,75 mmol/l neither at birth nor at 45 and 90 min of life. This was not surprising as neonatal Ins was always < 5 IU/ml well below the level at risk for neonatal hypoG(1). In addition neonatal AcAc at birth was by far higher in RL group (108 ± 45 vs 28 ± 12 µmol/l), which is explained by higher maternal AcAc in RL group as AcAc cross the placenta. AcAc can replace glucose for fetal and neonatal brain's metabolism allowing a better tolerance to hypoG(2). We believe that the stable and normal neonatal G of RL group was due to their higher level of AcAc.



Conclusion: Our study shows that glucose administered at a moderate rate of continuous infusion does not induce neonatal hyperIns or hypoG. However the lack of glucose in normal parturients in active labor under EA does not appear to be detrimental for maternal or neonatal G.

Reference: 1:Mendiola J, et al: Anesth Analg 1982; 61: 84-92. 2: Myers M E: Year book Medical 1978: 37-97

A.176

EPIDURAL CLONIDINE ANALGESIA AFTER MAJOR GYNAECOLOGICAL SURGERY

Ivan Smilov, Borislav Borissov

**University Hospital of Obstetrics and Gynaecology,
Sofia, Bulgaria**

Background and goal of study: After it has been established that clonidine may inhibit the release of substance P from the afferents in the spinal horn by mean of α_2-stimulation, the potential benefits of epidural clonidine on postoperative pain has been extensively studied. The present study was undertaken to elucidate whether epidural clonidine is effective in providing analgesia after gynaecological surgery.

Materials and methods: Twenty ASA class II patients undergoing radical hysterectomy were studied. An epidural catheter was placed preoperatively at the L1/L2 or L2/L3 level. After determination of correct placement by administration of a test dose, each patient received general anaesthesia. Sixty min after completion of surgery, 3 $mcg.kg^{-1}$ of clonidine were administered via the catheter. Postoperative pain was assessed by a visual analogue scale.

Results and discussion: The duration of pain relief acheived with epidural clonidine only lasted between two and five hours. Moderate hypotension which did not require iv volume or vasopressors accompanied the clonidine administration.

Conclusion: This study shows that epidural clonidine can provide satisfactory postoperative pain relief with an acceptable level of side effects.

Reference: Bonnet F, et al: Postoperative analgesia with epidural clonidine. Br J Anaesth 1989; 63: 465-9.

A.177

MECHANISMS OF ECG CHANGES DURING CAESAREAN SECTION (CS) - A HYPOTHESIS.

Mikael Svanström, Göran Johansson, Eva Bålfors.

Department of Anaesthesia, University of Umeå, Umeå, Sweden.

Background & goal of study: Recent studies have shown that 25 to 64% of women undergoing CS develop short-lived ECG changes, the configuration of which suggest an ischaemic origin (1). One other study has failed to confirm these data (2). As yet, there is no proof that the ECG changes represent myocardial ischaemia, neither has their cause been clarified. The goal of this study was to provide additional information on the time course of new spatial ECG changes in relation to systemic blood pressure variations and oxytocin administration in CS.

Patients & methods: After institutional approval and informed consent, 12 healthy women scheduled for elective CS under combined spinal/epidural anaesthesia were studied. Invasive blood pressure was recorded in 8/12. Computerized vectorcardiography (VCG) was used to detect electrocardiographic changes. STC-VM, e.g. the change of the spatial ST-vector magnitude was the ST-variable which was followed continuously. A change of STC-VM by more than 50 uV has previously been described as abnormal. Patients were kept in the left lateral tilt until delivery after which oxytocin was administered iv at 10 IU. Nasal oxygen was given and oxygenation monitored by pulse oximetry. Iv ephedrine was given as required to maintain systolic blood pressure above 95 mm Hg before delivery.

Results & discussion: 10/12 (83%) developed abnormal STC-VM changes (range 60 to 280 uV), which in all patients occurred within 60 sec (range 20 to 60 sec) of the oxytocin injection and were of short-lived duration (range 90 to 210 sec). All ST-changes were characterized by depression and were horizontal or downsloping. Heart rate was not significantly altered. 6/8 who had invasive blood pressure measurement displayed STC-VM changes. Diastolic blood pressure decreased in 7/8 (range 36% to 57%). The change of STC-VM correlated with the fall in diastolic blood pressure. We conclude 1. that iv oxytocin produced diastolic arterial hypotension, consistent with the vasodilating property of this drug (3), 2. this hypotension frequently caused marked ST-segement depression. We suggest that myocardial underperfusion due to hypotension and possibly increased coronary vasomototor tone by oxytocin (4) is responsible for the ECG changes. Further studies are needed to precisely determine the role of oxytocin in this respect.

References: 1. Palmer CM, et al: Anesth Analg 1990; 70:36, 2. Trotter TN, et al: Br J Anaesth 1992; 69:352, 3. Petty MA: J Auton Pharmacol 1987; 7:97, 4. Fortner CL, et al: J Pharmacol Exp Ther 1969; 165:258.

A.178

PROLONGED (> 1 WEEK) SEDATION WITH MIDAZOLAM IN ICU PATIENTS: EFFICACY, SAFETY AND PHARMACOKINETICS

L Heytens, L Bossaert

Department of Intensive Care, University Hospital, Antwerp, Belgium

Objective : to study the efficacy and safety of midazolam in very prolonged (at least 7 days) sedation of traumatized patients in a surgical Intensive Care Unit. Special attention was also given to the plasma concentrations during sedation and after the cessation of the midazolam infusion.

Methods : 12 patients 16 - 65 y with major chest trauma requiring prolonged ventilatory support were enrolled in the study (excluded were patients with head injury, hypotension, renal and liver failure). Sedation consisted of midazolam 5 mg/hr supplemented with fentanyl 2 µg/kg/hr. The dose was adjusted according to clinical need with a maximum midazolam dose of 0.2 mg/kg/hr.

The following variables were recorded : A 10 point Visual Analog Scale of agitation, pain and alertness every 4 hours; evaluation of the degree of sedation using a 4 point scale (1 = insufficient, 2 = moderate, 3 = good, 4 = unresponsive), speed of infusion of midazolam (mg/kg/hr) and plasma concentrations of midazolam (every 3 days during the study and at 4, 3, 2, 1 and 0 hours before termination of the midazolam infusion and 4, 8, 12, 16, 26, 48 and 72 hours after stopping the infusion).

Results : The mean duration of sedation was 18.9 ± 7.2 days. The quality of the sedation was considered 'unresponsive' in 40 %, good in 36%, moderate in 19% and insufficient in 5% of the evaluations. The mean midazolam dose had to be increased from a mean of 5.0 ± 0.0 mg/hr to 10.3 ± 3.6 mg/hr over the first week; an observation made in the majority of the patients. Steady-state plasma concentrations before termination of the infusion ranged from 0.31 - 2.47 µg/ml (mean 0.80 ± 0.79 µg/ml) dropping to 0.03 - 1.11 µg/ml (mean 0.22 ± 0.34 µg/ml) after 12 hours. Prolonged rest sedation (> 48 hrs) was observed in 1 patient and agitation, interpreted as withdrawal symptoms, in 8 patients.

Conclusions : These findings illustrate that a continuous infusion of midazolam/fentanyl can provide a good level of sedation for up to several weeks in the majority of these patients. The plasma concentrations of midazolam show large interindividual differences, even at the same level of sedation. A moderate degree of tolerance to either or both of the drugs used as well as withdrawal symptoms have to be anticipated.

A.179

INCIDENCE OF BACTERIAL MAXILLARY SINUSITIS IN CRITICALLY ILL PATIENTS WITH RADIOLOGIC MAXILLARY SINUSITIS.

L. Bodin, P. Laurent, T. Do-Khac, A. Zouaoui, G. Lamas, E. Cambau, J. J. Rouby, P. Viars.

Département d'Anesthésie-Réanimation. GH Pitié-Salpétrière Université Paris VI France

Introduction : Maxillary sinusitis frequently occurs in mechanically ventilated patients. The aim of this prospective study was to assess the incidence of bacterial maxillary sinusitis in intubated critically ill patients with radiologic maxillary sinusitis.

Methods: 127 mechanically ventilated patients (mean age : 56 ± 15 years) were prospectively enrolled in the study after informed consent and institutional approval was obtained. Within 48 hours following admission to the SICU, a paranasal CT scan demonstrated radiologic maxillary sinusitis defined as an air-fluid level opacity or a total opacification of the maxillary sinus. Within 24 hours following the CT scan, a transnasal puncture of maxillary sinuses was performed under general anesthesia, after desinfection of the nares. A nasal swab before and 20 minutes after a large desinfection of the nares using a polyvidone-iodine solution was performed for evaluating efficency of the nasal desinfection. Sinus contents were bacteriologically processed including cell count and quantitative analysis. A bacterial sinusitis was defined as the presence of altered polymorphonuclear leukocytes (> 5 per oil immersion field) associated or not with a positive culture. In case of inadequate desinfection of the nare (positive nasal swab after desinfection), high bacterial concentrations ($\geq 10^3$ cfu/ml and at least 10 fold greater than bacterial concentrations found in the nare) were required for the diagnosis of bacterial sinusitis.

Results : 194 maxillary sinuses were punctured in 127 patients (unilateral puncture n = 60, bilateral puncture n = 67). Desinfection of the nares was adequate in 91 cases (negative nasal swab after desinfection). According to cytologic and bacteriologic criteria, bacterial maxillary sinusitis was diagnosed in 51 patients. The incidence of bacterial maxillary sinusitis among patients with radiologic sinusitis was of 38%.

Conclusion: Radiologic maxillary sinusitis frequently occurs in intubated critically ill patients. However, these radiologic sinusitis are not always due to an infectious process since only 38% of our patients had cytologic and bacteriologic criteria demonstrating bacterial maxillary sinusitis.

A.180

REASSESSMENT OF BRONCHOALVEOLAR LAVAGE IN THE DIAGNOSIS OF POST TRAUMATIC PULMONARY FAT EMBOLISM

Olivier Mimoz, Alain Edouard, Laurent Beydon,
Françis Bonnet et Kamran Samii

Anesthésie Réanimation et Anatomo-Pathologie,
Hôpitaux de Bicêtre (F94275 Le Kremlin Bicêtre)
et Henri Mondor (F94010 Créteil)

Background and goal of the study: The importance of fat droplets within cells recovered by bronchoalveolar lavage (BAL) has been proposed as a rapid and specific method for establishing the diagnosis of post-traumatic pulmonary fat embolism (PFE) (1). However, the low value (5%) retained as the significant threshold may be questionable. Thus, the goal of the present prospective study was to compare the results of BAL with the clinical patterns of PFE in trauma patients.
Materials and methods: BALs were performed in 48 patients (age: 33±16 yrs, ISS: 39±13, SAPS: 11±3, mean ± SD) during the first 3 days after trauma to determine the percentage of lavage cells containing intracellular fat droplets. On the 5th post-traumatic day, patients were included into one of 3 groups according to the presence or not of the 3 major features of the fat embolism syndrome described by Gurd (2) (F1: petechial rash, F2: ARDS, F3: neurological disorders). PFE was considered as definite when 2 out of 3 major features were observed (the presence of F1 is mandatory in cases of associated thoracic or cranial trauma), likely when F2 or F3 were present, but could be explained by a specific injury (pulmonary contusion, cranial trauma) and unlikely in the other cases. At that time, the attending physician was unaware of the BALs' results. BAL was done and analyzed as previously described by Chastre et al (1). Fat droplets were stained with Soudan 3.
Results: the percentage of lavage cells containing intracellular fat droplets for the 3 groups of patients is shown in this table.

clinical PFE		% of cells containing fat droplets				
	n	0-5	6-29	30-49	50-69	70-100
Definite	4	0	0	0	0	4
Likely	4	1	0	1	1	1
Unlikely	40	20	14	4	2	0

Conclusion: This study documents that a high percentage (>70%) of lavage cells containing intracellular fat droplets is observed when PFE is clinically obvious. In questionable cases or when PFE is unlikely, BAL fails to contribute to the diagnosis.

References: (1): Chastre et al: Bronchoalveolar lavage for rapid diagnosis of the fat embolism syndrome in trauma patients. Ann Intern Med 1990; 113: 583-588.
(2): Gurd AR: Fat embolism: an aid to diagnosis. J Bone Jt Surg 1970; 52B: 732-737.

A.181

HISTOLOGIC ASPECTS OF PULMONARY BAROTRAUMA IN CRITICALLY ILL PATIENTS WITH ACUTE RESPIRATORY FAILURE

Rouby J. J., Lherm T., Martin de Lassale E., Poete P.,
Bodin L., Viars P.

Département d'Anesthésie-Réanimation,GH Pitié-Salpêtrière,
Université Paris VI. France.

Introduction : Histologic studies on human lungs were performed to provide a comprehensive description of lung barotrauma in patients with ARDS requiring prolonged mechanical ventilation.

Methods: The lungs of 30 ARDS patients (mean age 34 ± 10 years) who died after a period of mechanical ventilation > 48 hrs, were histologically examined in the immediate postmortem period. Patients suspect of emphysema at the time of admission to the SICU and patients over the age of 50 were excluded. Characteristics of mechanical ventilation were prospectively recorded and compared with lung histology.

Results: One third of the patients presented one or several episodes of pneumothorax while on mechanical ventilation. At autopsy, pleural cysts of varying size (0.5 to 4 cms), airspace enlargement – defined as the presence of emphysema and/or intraparenchymal pseudocysts – and bronchiolar dilatation were found in 26 of the 30 lungs examined (86%). Mild airspace enlargement (1 to 2.5 mm internal diameter) were observed in 12 lungs and severe airspace enlargement (2.6 to 40 mm internal diameter) were found in 14 lungs. Patients with severe airspace enlargement had a significantly greater incidence of pneumothorax (8 vs 2, $p < 0.05$), were ventilated using higher peak airway pressures (56 ± 18 cm H_2O vs 44 ± 10 cm H_2O, $p < 0.05$) and tidal volumes (12 ± 3 ml/kg vs 9 ± 2 ml/kg, $p < 0.05$), were exposed significantly longer to toxic levels of oxygen (8.6 ± 9.4 days vs 1.9 ± 2 days at $FiO_2 > 0.6$, $p < 0.05$) and lost more weight (6.3 ± 9.2 kg vs 0.75 ± 5.8 kg, $p < 0.05$) than patients with mild airspace enlargement.

Discussion: Histologic lesions characterizing lung barotrauma consist of pleural cysts, bronchiolar dilatation, emphysema-like lesions and intraparenchymal pseudocysts. Mechanical ventilation could be a causative factor, particularly when high peak airway pressures and large tidal volumes are delivered to the lungs.

A.182

COMPARAISON OF PRESSURE SUPPORT VENTILATION PROVIDED BY TWO ICU VENTILATORS

Kalfon P., Rouby J.J., Viars P.

Département d'Anesthésie-Réanimation.
GH Pitié-Salpêtrière Université Paris VI, France

Introduction: Quality of pressure support (PS) ventilation provided by the CESAR ventilator (TAEMA, France) and by the BIRD 8400 ST ventilator (BIRD, USA) were compared.
Patients and methods: Four patients in the process of weaning from mechanical ventilation were studied. For each ventilator, at 4 PS levels (+ 5, + 10, + 15, + 20 cmH20), and for the same trigger (- 1 cm H20), tidal volume (Vt), gas flow (V), esophageal pressure (PES), intratracheal pressure (PAW), and pressure in the ventilator (PV) were recorded. The following parameters were measured : delay between the beginning of inspiration and the time when PV becomes positive (Tor), negative peak pressure of PV, trigger value (Pt), delay between valve opening and obtention of a PV-plateau (Tpl), PV-plateau (Ppl), end-inspiration PAW value (Paw), PAW value at the obtention of the PV-plateau (Pawpl), inspiratory total tidal volume (Vti), inspired volume at the obtention of the PV-plateau (Vtipl), and maximal inspiratory flow (Vmax).
Results: Tor was shorter with the BIRD (98 $^+$ 22 ms) than with the CESAR (162 $^+$46 ms), whatever the PS level. Pt was less negative with the BIRD (- 1.54 $^+$ 0.4 cm H20) than with the CESAR (-2.2 $^+$0.5 cm H20). Ppl differed from the selected PS level : superior with the BIRD, inferior with the CESAR. Tpl was longer with the BIRD than with the CESAR. With both ventilators, no PAW plateau was identified. PAW was close to Ppl for both ventilators, but Pawpl and Pawpl/Paw were higher with the BIRD than with the CESAR. Vti was superior with the BIRD than with the CESAR. Vti and Vtipl/Vti were higher with the BIRD than with the CESAR, whatever the PS level.
Conclusion: Quality of the PS ventilation was evaluated according to 3 criteria : 1) concordance between the selected PS level and the delivered PS level. 2) quality of the inspiratory valve, appreciated by the opening delay and the negative peak pressure in the ventilator. 3) respective aspects of pressure curves in the ventilator and in the trachea. The application of these criteria showed that PS provided by the BIRD ventilator was slightly better than PS provided by the CESAR ventilator. However, with both ventilators, no plateau was obtained within the trachea. A standardization of the evaluation procedures of PS ventilation should permit an accurate comparison of the different avalaible ICU ventilators.

A.183

EVALUATION OF CARDIAC FUNCTION IN ICU : RIGHT HEART CATHETERIZATION *VS* TRANSESOPHAGEAL ECHOCARDIOGRAPHY

Preliminary results

Benoît Vivien, Eric Mourgeon, Michel Saada, Jean-Pierre Goarin, Jean-Jacques Rouby, Pierre Viars

Département d'anesthésie-réanimation, Groupe Hospitalier Pitié-Salpêtrière, Université Paris VI, France

Background and goal of the study: Pulmonary artery catheterization (PAC) is commonly used in ICU to evaluate the hemodynamic status of unstable patients. Recently, transesophageal echocardiography (TEE) has been introduced in ICU for the same purpose. Thus, we prospectively compared both techniques for assessment of hemodynamically unstable patients.
Material and methods : Eighteen consecutive patients admitted in ICU were included. Mean arterial, pulmonary arterial, and capillary wedge pressures, systemic resistance, and cardiac output were obtained using PCA. TEE gave informations on preload (derived from end-diastolic area) and left ventricular (LV) function (derived from LV ejection fraction and LV wall thickening). PAC and TEE were performed and analyzed by 2 different highly-trained experts blinded from each other about their respective hemodynamic evaluation. The following hemodynamic diagnosis could be made : 1) hypovolemia or normovolemia 2) decreased or normal LV function.
Results: Concerning volemia, PAC and TEE concorded in 11 cases. In 5 cases, TEE diagnosed hypovolemia whereas the patients were considered normovolemic by PAC Reciprocally, 2 cases were considered normovolemic by TEE whereas hypovolemia was diagnosed by PAC. The discordance was thus 39% for estimating volemia. Concerning LV function, PAC and TEE concorded in 14 cases. In the remaining 4 cases, TEE diagnosed a decreased LV function whereas it was considered normal by PAC. No patient who exhibited a decreased LV function by PAC was found to have a normal LV function using TEE. The discordance was thus 23% for estimating LV function. Beside this comparison, TEE brought new diagnostic elements in 11 cases: segmental wall motion abnormalities (n=9), mitral cordage dysfunction (n=1), right ventricular pseudoaneurysm (n=1), and voluminous pleural effusion (n=2).
Conclusion : Since TEE is considered to be the gold standard for the assessment of preload and global LV function, this study showed that PCA may be inaccurate in 39% of cases for the assessment of volemia, and in 23% of cases for the assessment of LV function in ICU hemodynamically unstable patients.

A.184

INFLUENCE OF NOREPINEPHRINE THERAPY ON THE OXYGEN SUPPLY AND LACTATE EXTRACTION RATE OF THE LIVER IN THE SEPTIC PIG

Reiner Schäfer*, Werner Gerling*, Angela Utschakowski+, Klaus Wagner#

*Klinik f. Anästhesiologie, +Klinik f. Chirurgie, #Inst. f. Physiologie, Medizinische Universität Lübeck, W-2400 Lübeck, Bundesrepublik Deutschland

Background and goal of study: Little is known about oxygen delivery and consumption in the septic state under experimental conditions in animals, if circulation is hold up as it is done in human patients, i.e. with therapy like norepinephrin and volume. Therefore this study was performed to investigate the influence of norepinephrine in the treatment of the early septic shock on the oxygen consumption and function of an important organ like the liver.

Materials and methods: After government approval we used 16 female domestic pigs between 20 and 28 kg body wt.; 6 pigs without sepsis served as control group. Anesthesia was induced by ketamin/diazepam and maintained by thiopental, fentanyl and pancuronium. Sepsis was induced by E.coli.-endotoxin (0.25-0.5 µg/kg bw, 0.025µg/kg bw/min; infusion was stopped at PAP>60mmHg) and treatment with norepinephrine (0.1 - 2µg/kg bw/min by perfusor) was performed until MAP was >80mmHg. Central venous pressure was held between 5 and 10 mmHg by infusing ringer lactate and/or hydroxyethylstarch. The following values were measured before and after induction of sepsis: Cardiac output (CO, thermodilution), MAP, PAP, A.hep.flow, V.porta flow (electromagnetic/doppler-ultrasound flow probes), systemic and hepatic oxygen consumption, liver tissue pO_2 (needle electrode, polarographically) and lactate extraction rate. Measuring cues were before, 20, 40, 60, 90 and 120 min after induction of sepsis.

Results and discussion: Sepsis treated with Norepinephrin increased CO to 137 % of control, SVR decreased to 64 %. Systemic oxygen consumption increased to 126 %, liver oxygen consumption rested 95% of control values. The flows of the hepatic artery increased to 146 %, whereas the flows of the portal Vene decreased to 63 % of control. The ratio Flow hepatic artery/CO remained constant (about 9 %) throughout sepsis whereas portal venous flow/CO decreased. Liver tissue pO2 remained stable at 35 mmHg. Lactate extraction rate remained also stable at 0.45 mmol/100g liver tissue/min..

Our results suggest that treatment of early sepsis by norepinephrine does not influence oxygen delivery and consumption. The ability to extract lactate is also not depressed. The decrease of portal venous flow perhaps induced by alpha-receptor agonism in the splanchnic circulation is balanced by an increased oxygen extraction and a greater arterial oxygen delivery. The effectiveness of this mechanism is also supported by the stability of the tissue-pO_2-levels. Hepatic arterial vessels seem not to be influenced by norepinephrine.

Reference: Breslow J.M. et al: Effect of vasopressors on organ blood flow during endotoxin shock in pigs. Am.J.Physiol. 1987 H291-300

A.185

THE EFFECT OF DOBUTAMINE AND NOREPINEPHRINE ON GLOBAL AND SPLANCHNIC O_2 CONSUMPTION

Andreas Meier-Hellmann, Lutz Hannemann, Daniel Weyandt,Wolfgang Heiss-Dunlop, Konrad Reinhart

Dept. of Anesthesiology and Surgical Intensive Care Medicine, Steglitz Medical Center, Free University Berlin, FRG

Background and goal of study: Dobutamine (DOB) alone or in combination with norepinephrine (NE) is considered to achieve higher O_2 transport (DO_2) levels and better tissue oxygenation than norepinephrine alone in patients with septic shock, . To prove this we investigated the effect of these two regimens on DO_2, whole body oxygen uptake (VO_2) and splanchnic perfusion (HBF) as well as splanchnic O_2 uptake (VO_{2hep}).

Materials and methods: After approval by our local ethics committee and after obtaining informed consent, 10 patients with septic shock needing inotropic support and vasopressors despite adequate volume loading (PCWP >15 mmHg)were investigated. A 7.5 F catheter was inserted into the hepatic vein. 6 patients were initially treated with DOB combined, if necessary, with NE titrated to maintain a mean arterial blood pressure (MAP) above 70 mmHg. At 0, 60 and 120 minutes, hemodynamic measurements including the oxygen transport related variables and hepatic venous O_2 saturation were performed. Hepatic blood flow (HBF) was determined by the ICG dilution technique. After two hours the regime was changed to NE alone (in a dosage to achieve the same MAP as before), thereafter the same measurements as before were performed. The remaining 6 patients were managed in the reverse order. Statistics: Wilcoxon test for dependent samples ($p < 0.05$).

Results and discussion: The results are given in the table.

	DOB/NE	NE	
DO_2 ml/min/m^2	796 ±151	598 ±113	*
VO_2 ml/min/m^2	159 ±27	152 ±26	n.s.
CI l/min/m^2	6.0 ±1.2	4.3 ±0.8	*
DO_{2hep} ml/min/m^2	210 ±108	171 ±88	*
VO_{2hep} ml/min/m^2	77 ±41	72 ±21	n.s.
HBF l/min/m^2	1,6 ±0.8	1.1 ±0.6	*
DO_2 / DO_{2hep}	4.3 ±1.4	4.1 ±1.7	n.s.
VO_2 / VO_{2hep}	4.9 ±2.5	4,8 ±1.3	n.s.
CI / HBF	4.3 ±1.4	4.1 ±1.7	n.s.
SvO_2 %	76 ±4	71 ±6	*
$ShvO_2$ %	58 ±13	49 ±15	*

CI: cardiac index, SvO_2: mixed venous O_2 saturation. $ShvO_2$: hepatic venous O_2 saturation, * : $p < 0,05$, n.s.: not significant, values are given as mean ± SD

The parallel decrease in DO_2 and DO_{2hep} did not result in a decreased VO_2 and VO_{2hep}. This indicates that oxygen consumption did not become supply dependant in the whole body or the splanchnic region. The unchanged CI/HBF indicates that there was no redistribution of blood flow at the expense of the splanchnic region. We conclude that whole body and splanchnic tissue oxygenation was not compromised with NE alone. The decrease in DO_2 and DO_{2hep} was compensated for by an increase in O_2 extraction.

A.186

INFLUENCE OF N-ACETYLCYSTEINE ON O_2 CONSUMPTION AND GASTRIC INTRAMUCOSAL PH IN SEPTIC PATIENTS

C. Spies, I. Witt, C. Walensky, L. Hannemann, K. Reinhart

Department. of Anesthesiology and Intensive Care Medicine, Steglitz Medical Center, Free University Berlin, Berlin, Germany

Background and goal of study: Endothelium-derived relaxing factor (EDRF) might be important in maintaining microcirculatory blood flow in critically ill patients but its full activity might not be sustained because of the depletion of tissue sulhydryl groups. N-acetylcysteine (NAC) by replenishing tissue sulfhydryl groups could restore the full activity of EDRF. We investigated whether NAC would be of benefit in septic patients with multiple-organ failure.
Materials and methods: 38 septic patients, requiring extended hemodynamic monitoring (radial and pulmonary artery catheter) were included in this randomized, institutionally approved study. A gastric tonometer was inserted to assess nutritive blood flow to the mucosa by measuring gastric intramucosal pH (pHi). Written informed consent was obtained from the relatives. Patients received either 150 mg/kg NAC or placebo over a period of 20 minutes. Measurements were obtained before treatment (baseline), after 30 minutes of infusion (infusion), and 2 hours after infusion (recovery). Statistical analysis was performed by the Wilcoxon signed rank-sum test and adjusted for Bonferroni's method.
Results and discussion: Baseline and recovery measurements were not significantly different between groups. After infusion of NAC O_2 consumption (VO_2), O_2 delivery (DO_2), cardiac index, and O_2 extraction ratio (O_2ER), as well as pHi significantly increased in 9 patients of the NAC group (responder). In the other 10 patients of the NAC group (non-responder) as well as in the placebo group all parameters remained stable. In the NAC group 11 patients, in the placebo group 5 patients survived.
Conclusion: Some patients showed an improvement in VO_2, O_2ER, and pHi after NAC infusion which might be consistent with an improvement in microcirculatory blood flow. Whether survival is improved requires further investigation.

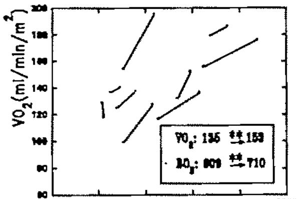


Fig.1: Responder of the NAC group
($VO_2 = O_2$ consumption, $DO_2 = O_2$ delivery)

A.187

MOLECULAR MEDIATORS AND POST-BACTERAEMIC PHASE

K Martínez Urionabarrenetxea, JL Pérez Arancón, JI Yoldi, A Camarero, JL Martínez

Intensive Care Units, Hospital de Navarra, Pamplona, Spain

INTRODUCTION.- It is well known that TNF acts as a mediator in shock and organ disfunction during sepsis(1). Its metabolism makes its study difficult in non-shocked septic patients (2). This prospective study was performed to evaluate changes in blood levels of TNF and PAI-1 in post-bacteriemic states.

METHODS.- Twenty patients, who accomplised inclusion criteria as septic were studied. Inclusion criteria were: evidence of septic focus; no bacteriemic sign two hours before blood extraction; hemodynamic stability; leukocytosis and/or inmature leukocytes. Mean organ disfunction was 3 organs, extremes ranging from 2 to 6.

To estimate the variability of TNF and PAI-1 values, a group of 24 volunteers during their usual work was analyzed.

RESULTS.- The analysis of TNF and PAI-1 values in patients related to controls shows significant difference for both mediators.

TNF	**Mean±St Error**	p
Controls	1,62±0,44	
Patients.	55,09±1,44	0,001

PAI-I	**Mean±St Error**	p
Controls	14,16±1,56	
Patients	19,86±1,91	0,05

COMMENTS.- Monocytic system reponds to infection intensely producing TNF during the two first hours, to saty refractary to new stimuli for the next 8 hours, but with slighlty high levels. The endotehlium is stimulated by TNF to release PAI-1, which reaches peak level 3 hours later and returns to basal values in 24 hours.

This study shows elevations of TNF during the refractary period and of PAI-1 before the 24 hours after the bacteriemic phase.

CONCLUSIONS.- TNF and PAI-1 are indicators of infection in the post-bacteriemic phase.

References: 1) Debets JMH. Plasma tumor necrosis factor and mortality in critically ill septic patients. CCM 1989; 17:489-494. 2) Suffredini A. Promotion and subsequent inhibition of plasminogen activation after administration of intravenous endotoxin to normal subjects. N. Engl. J. Med. 1989; 320: 1165-1172.

A.188

MOLECULAR MEDIATORS AND CARDIAC SURGERY

**JL Pérez Arancón, K Martínez Urionabarrenetxea,
JI Yoldi, A Camarero, JL Martínez**

Intensive Care Units, Hospital de Navarra, Pamplona, Spain

INTRODUCTION.- It is well known that infection induces the release in plasma of high levels of TNF and other cytokines. TNF itself stimulates the release of PAI-1, which may independently reach very high levels in any inmediate post-surgiral state.

The elevation of TNF and PAI-1 blood levels in patients with no infectious pathology undergoing cardiac surgery has been described, thus invalidating these parameters as diagnostic data of infection in these patients.

This prospective study was performed to evaluate changes in plasma concentrations of TNF and PAI-1 in patients undergoing open heart surgery.

METHODS.- Twenty patients undergoing open heart surgery with extracorporeal circulation, and who accomplished inclusion criteria as non septical were studied.

To estimate the variability in TNF and PAI-1 plasma levels, a group of 24 volunteers in their usual work was analyzed.

Inclusion criteria were: absence of infection; no evidence of septic focus; subsystems'stability; no leukocytosis and/or leukopenia.

RESULTS.- The analysis of TNF and PAI-1 values in surgical patients related to controls shows significant difference for both mediators.

TNF	Mean±St Error	p
Controls	1,62±0,44	
Pat. Art.	72,06±26,08	0,001
Pat. Ven.	65,36±21,37	0,001

PAI-I	Mean±St Error	p
Controls	14,16±1,56	
Pat. Art.	21,31±2,16	0,01
Pat. Ven.	21,36±2,1	0,05

No significant difference was found between arterial and venous TNF and PAI-1 levels in the patient group.

CONCLUSIONS.- High levels of TNF and PAI-1 in inmediate extracorporeal cardiac surgery are not suggestive of infection.

Absence of arterio-venous differences in the values of both mediators is an indirect parameter of metabolic normality.

Reference Westaby S. Organ dysfunction after cardiopulmonary bypass. A sistemic inflammatory reaction initiated by the extracorporeal circuit. Intensive Care Med. 1987; 13: 89-95.

A.189

SEPTIC SHOCK : EFFECT OF A GOAL-DIRECTED THERAPY ON OXYGEN METABOLISM AND SERUM CYTOKINE LEVELS

Claude MARTIN, Pierre SAUX, Jean-Louis MEGE,
Gilles PERRIN, François GOUIN

Department of Anesthesia and intensive Care.
Hôpital Nord and Hôpital Sainte-Marguerite
13009 MARSEILLE - FRANCE

Background and goal of study : achieving and maintaning optimal hemodynamic and metabolic patterns have been suggested to improve survival of critically ill septic patients (1, 2). The present study was designed to prospectively evaluate the effects of such a goal-directed therapy on oxygen-derived parameters (Oxygen delivery - DO2, Oxygen uptake - VO2) and serum cytokine levels in septic shock patients.

Materials and methods : thirty consecutive patients (56 ± 20 years, APACHE II Score 31 ± 1) were prospectively studied. All patients were mechanically ventilated for ARDS or severe pneumonia. Different modes of therapy (fluid loading, dobutamine, norepinephrine and dopamine) were used to achieve and maintain at the same time all of the following : Mean Systemic Arterial Pressure ≥ 80 mmHg (and/or Systemic Vascular Resistance Index between 1,100 and 1,300 dyn.sec/cm5.m2), IDO2 ≥ 550 ml/min/m2, IVO2 ≥ 150 ml/min/m2 and Cardiac index ≥ 4.0 l/min/m2. The aim of therapy was to fullfilled these previously determined goals for at least 24 hours and to restore and maintain normal urine flow (≥ 0.7 ml/kg/h whenever possible). Hemodynamic and oxygen derived parameters were checked every 4 hours and therapy was reevaluated according to the therapeutic goals. Serum lactate and cytokine (TNFα and IL6) levels were also determined. The predicted mortality was obtained using the APACHE II scoring system.

Results and discussion : The therapeutic goals were achieved and maintained for at least 24 hours in all but two patients (93 %). Twenty four patients (80 %) survived the episode of septic shock and 6 (20 %) died in intractable shock. Nine patients subsequently died from Multiple Organ Failure and 15 patients were eventually discharged from the hospital. The overall hospital mortality (50 %) was significantly lower than the APACHE II predicted mortality : 80 % (p <0.02). The table shows that in the survivors (S) a significant increase in IDO2 and IVO2 was observed throughout the first 24 hours. No such improvement was seen in patients who died in shock (D) or from organ failure (MOF). lactate levels exhibited a significant decrease from the 6th hour on, only in survivors and MOF patients Serum TNF levels exhibited a significant decrease from the 6th hour on, only in the survivors. In MOF patients, serum TNFα levels remained elevated which was in contrast with the improvement observed in their hemodynamic condition and serum lactate levels. A similar and progressive decrease in serum IL6 levels was observed in the three groups.**Conclusion :** An improvement of oxygen utilization was seen only in survivors. The decrease in serum TNFa levels was significantly associated with a favorable outcome. Moreover, a goal-directed therapy aimed at improving hemodynamic and metabolic conditions of septic shock patients may substancially reduce mortality **References :** 1. Chest 94:1176-1186, 1988 2.Crit Care Med 17:1098+1103, 1989

	before			6 hours			24 hours			48 hours	
	S	D	MOF	S	D	MOF	S	D	MOF	S	MOF
IDO_2 ml/ min/m²	657 ±250	421 ±96	671 ±177	743* ±250	538 ±189	613 ±82	783* ±259	530 ±240	602 ±47	694 ±174	650±1 43
IVO_2 ml/ min/m²	158 ±94	142 ±41	155 ±62	189* ±55	174 ±28	153 ±41	217* ±66	181 ±62	156 ±26	181* ±47	173±3 5
lactate mmol/l	4.1 ±1.6	8.6+ ±6	4.4 ±2	3 ±1	10* ±9	3.7 ±1	2.4* ±1	12* ±10	3.1* ±1.8	2* ±0.6	3* ±1.5
TNF pg/ml	27 ±9	49 ±14	61 ±27	17 ±3*	44 ±18	39 ±10*	11 ±3*	46 ±17	28 ±7*	12 ±3*	39 ±2

Table *p<0.01 – +p<0.05

A.190

COMPARISON OF TWO THERAPEUTIC STRATEGIES OF SEPTIC SHOCK

Claude Martin, Jean-Pierre Auffray, Frédéric Potié,
François Gouin.

Hôpital Nord et Hôpital Sainte-Marguerite
Marseille - France

Background and goal of study : the optimal therapy of septic shock remains a matter of controversy.
Materials and methods : from january 1988 to january 1992, two therapeutic strategies were prospectively evaluated in 129 patients with septic shock. In group 1 (72 patients) all patients had a Swan-Ganz catheter and an arterial catheter inserted. Hemodynamic parameters (measured and calculated), oxygen-derived parameters (oxygen delivery - IDO2 - and uptake - IVO2), blood lactate, arterial and mixed-venous blood gas analysis were obtained every 4 hours (or more when needed). Based on the results, appropriate treatments (fluid infusion, vaso-active agents) were selected and the goals were to achieve and maintain all of the following : cardiac index ≥ 4 l/min/m2, vascular resistance > 1100 dyne.sec/cm5.m2 and / or mean arterial pressure (MAP) ≥ 80 mmHg, IDO2 > 550 ml/min/m2, IVO2 > 150 ml/min/m2, urinary flow (UF) ≥ 0.7 ml/kg/h. In group 2 (57 patients) patients had a central venous line and an arterial catheter inserted. Vital signs were obtained every hour. The aim of therapy was to achieve and maintain MAP ≥ 80 mmHg and UF ≥ 0.7 ml/kg/h. In both groups, patients were mechanically ventilated and SpO2 was maintained > 95%. The choice of therapy was based on the physician's preference.
Results and discussion : both groups were similar with regard to : age (56 ± 17 and 58 ± 17 years), sex-ratio (males : 75% and 68%), APACHE II score (29 ± 3 and 27.5 ± 3), peritonitis (35% and 40%), pneumonia (53% and 47%), appropriate antibiotic therapy (80% and 70%), dobutamine (60% and 58%). More patients received norepinephrine in group 1 (100% vs 58%, p < 0.01) and dopamine in group 2 (65% vs 36%, p < 0.01). Therapeutic goals were simultaneously fulfilled for 24 hours in 92% of patients in group 1. In group 1, hospital mortality was 53% and 86% in group 2 (p < 0.001).
Conclusion : the present study was neither blinded nor randomized.However, the results suggest that a goal-directed therapy based on hemodynamic and metabolic parameters may significantly reduce hospital mortality of patients with septic shock.

A.191

NON INVASIVE MONITORING OF CO_2 IN PATIENTS WITH SEPTIC SHOCK

L. Bodin, H. Maghrebi, C. Kaddour, M. Arthaud,
J.J. Rouby, P. Viars.

Département d'Anesthésie–Réanimation GH Pitié–Salpêtrière.
Université Paris VI. France

Introduction : Two methods are available for $PaCO_2$ monitoring : end–tidal carbon dioxyde tension (Pet CO_2) and transcutaneous CO_2 (Ptc CO_2). The aim of this study was to evaluate capnometry and transcutaneous CO_2 monitoring in critically ill patients with septic shock and ARDS.
Methods: Seven critically ill patients with septic shock and ARDS were prospectively studied. Patients with brain injury, pulmonary embolism, or coronary artery disease were excluded. $PaCO_2$ was measured using a Blood Gas Analyser. Pet CO_2 was measured using a non aspirative capnometer (Hewlett–Packard HP 47210A). Ptc CO_2 was measured using a Critikon Fas–Trac and a sub–clavicular probe. Every 6 hours, calibration was performed and the site of the probe was changed. For each patient, 3 tidal volumes (VT) of 5,10 and 14 ml/kg were randomly applied in order to modify $PaCO_2$. Seventy simultaneous measures of $PaCO_2$, Pet CO_2 and Ptc CO_2 were performed after a steady state was obtained for a given VT. Differences between $PaCO_2$ and Pet CO_2 and between $PaCO_2$ and Ptc CO_2 were calculated for the different values of $PaCO_2$. Bias and precision determinations were calculated using the method of Bland and Altman (1).
Results: Results are shown on figures 1 and 2. Bias and precision were respectively of – 9 mmHg and 6 mmHg for the capnometer and of – 2.5 mmHg and 2.7 mmHg for the Ptc CO_2.
Discussion : This study shows that in patients with septic shock, Ptc CO_2 remains an accurate method for monitoring $PaCO_2$. In contrast, Pet CO_2 markedly underestimates $PaCO_2$.
Reference: (1) Bland J., Altman A. Lancet 1986. 8 : 307–310.

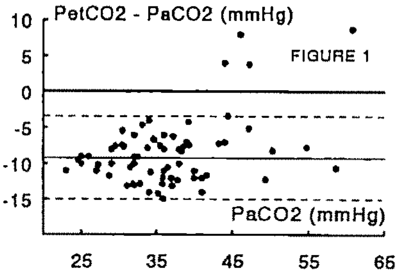


FIGURE 1

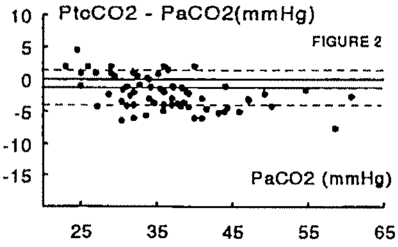


FIGURE 2

A.192

EVALUATION OF SYSTEMATIC TEE IN PATIENTS SUSPECTED OF BLUNT CHEST TRAUMA.

P.Catoire*, L.Delaunay*, L.Beydon*, P.Guerrini*, F.Bonnet*.

*Réanimation chirurgicale, hôpital Henri Mondor, CRETEIL; FRANCE.

Background and goal of the study: Intra-thoracic lesions can be missed after blunt chest trauma (BCT) because appropriate diagnostic tools are invasive and therefore can not be systematically used. TEE is a non-invasive technique allowing the diagnosis of intra-thoracic lesions in a selected population of patients with widening of the mediastinum on chest X-ray after blunt chest trauma (1). We carried out a prospective study in order to evaluate TEE in patients suspected of BCT.

Material and methods: Thirty six patients were included in this prospective study. Patients suspected of BCT because of a violent shock, a rapid deceleration after a traffic crash or a fall, were scheduled for TEE. All of them were intubated, under controlled ventilation. We used a Diasonics ® CFM 750 echocardiograph with a 5 MHz transesophageal probe. TEE examination was performed within 48 hours following admission. The results of TEE were compared to informations obtained on admission from clinical examination, chest X-ray, 12 leads ECG and CK-MB plasma concentrations.

Results and discussion: Patients mean severity score index was 31±11. None of the patients had a significant cardiac enlargement on chest X-ray. Myocardial contusion was suspected in 14 cases (12 ECG abnormalities, 3 increases in CK-MB). TEE docu-mented segmental wall motion abnormalities or altered global function in 8 patients (22%). In addition, TEE found out unexpected thoracic lesions in 11 patients (30%) including 8 pericardial effusions, one tricuspid and one mitral valve regurgitation, and one ascending aortic intimal tear. Four of these patients had no clinical evidence for chest trauma. In three patients, severe hypovolaemia was asserted (ITDA≤ 5cm^2). Moreover, 9 pleural effusions and 5 lung conden-sations were documented on TEE and confirmed by CT scan. TEE diagnosis allowed an immediate specific treatment in 5 cases leading to a dramatic inprovement of patients condition.

Conclusion: TEE must be systematically performed in multiple trauma patients when BCT is suspected. It allows to discover intrathoracic lesions which may justify an appropriate treatment in a significant number of cases.

(1)Shapiro MJ: Cardiovascular evaluation in blunt thoracic trauma using TEE. J.Trauma,1991; 31: 835-39.

A.193

DIAGNOSIS OF AORTIC RUPTURE BY TRANSESOPHAGEAL ECHOCARDIOGRAPHY (TEE)

J.P. Goarin, F. Le Bret, Y. Jacquens,
B. Riou, M. Saada, P. Viars
Department of Anesthesiology.
CHU Pitié-Salpêtrière. Paris. France

Backgrounds and aim of the study. Blunt chest trauma, occurring during high-speed deceleration accidents, can be associated with aortic rupture. Prognosis depends on prompt diagnosis and surgical treatment. Angiography is the routine procedure, nevertheless this method is time consuming, invasive and can be hazardous for patients with multi system injuries and unstable hemodynamic status. Some studies have demonstrated the accuracy of TEE for spontaneous aortic dissection diagnosis (1). The aim of this study is to evaluate TEE in traumatic aortic lesion.

Patients and methods. TEE was performed in all patients with blunt chest trauma to assess the hemodynamic status and to detect intra-thoracic lesions (aortic rupture, myocardial contusion, pericardial, mediastinal and pleural effusions). We used a Hewlett-Packard Sono S500 with a single plane transesophageal probe. TEE were recorded on video-tape for retrospective cross examination by an undependant observer. The results were compared with angiographic and intraoperative findings.

Results. During a 26 months period, 37 patients had both TEE and angiography.

8 presented a traumatic aortic lesion : 5 had a false-aneurysm localized to the isthmus, associated for 3 of them, with a dissection of descending aorta. 3 patients had a rupture limited to the intimal part of the aortic wall.The diagnosis could have been made immediately in 6 cases and in one more case after reviewing the video-tape. In one case TEE was considered normal. Angiography and TEE were confirmed by operative findings.

TEE Angio	Positive	Negative	Uncertain*
Positive	6	1	1
Negative	0	28	1
Uncertain	0	0	0

* The diagnosis was considered uncertain when the examiner and the independent observer disagreed.

Conclusion. Sensitivity and specificity is hard to define on a retrospective study but we can conclude already that TEE can provide (6/8 cases) a rapid diagnosis of aortic rupture with no need for further investigation in emergency situation.

(1) Echocardiography in diagnosis of aortic dissections. Erbel R., Lancet, 1 : 457, 1989

A.194

SYSTEMIC GAS EMBOLISM IN PULMONARY CONTUSION DIAGNOSED BY TRANSESOPHAGEAL ECHOCARDIOGRAPHY

Michel Saada, Bruno Riou, Jean-Pierre Goarin,
Jean-jacques Rouby, Yves Jacquens, P. Viars.
Department of Anaesthesiology,
CHU Pitié-Salpêtrière, Paris, France

Background: Systemic gaz embolism has been described following penetrating lung injury (1) and acute respiratory distress syndrome (2) in adults and children, but has never been reported in pulmonary contusion related to severe blunt trauma. We observed 4 patients with suspicion of systemic gas embolism following severe blunt thoracic trauma induced pulmonary contusion. Two out of 4 were demonstrated by transesophageal echocardiography (TEE). We report in the following abstract one of these 4 patients.

Patients and methods: A 27 y.o. man was admitted in a level 1 Trauma Center after a motorcycle accident. On arrival, the patient had complete paraplegia secondary to spinal cord injury at T4 level, thoracic trauma with multiple rib fractures and pulmonary contusion, and left leg fracture. During peripheral orthopedic surgery, severe hypotension was noted, associated with a significant decrease in SaO2 and endtidal CO2. Fat embolism was suspected and TEE was performed which showed a normal global and segmental left ventricular function and massive air embolism in the left heart coming from the pulmonary veins and rythmed by mechanical ventilation. During apnea, no more bubbles were observed. Patients recovery was complete without neurologic sequelae secondary to gas embolism.

Discussion: Systemic gas embolism can occur after sever pulmonary contusion and its incidence is probably underestimated. It can be aggravated during mechanical ventilation due to overdistension of the lung secondary to large tidal volume, resulting in an interstitial and alveolar edema and ruptured capillaries. Such events may happen during mechanical ventilation in patients with pulmonary contusion.Thus it should be recommanded to reduce tidal volume, to avoid PEEP, and possibly to use high frequency Jet ventilation in order to decrease the mean airway pressure.

References: 1. Graham J.M. et al : Systemic air embolism following penetrating trauma to the lung. Chest, 72 : 4, 1977. 2. Marini J.J. et al : Systemic gas embolism complicating mechanical ventilation in the adult respiratory distress syndrome. Annals of Intern. Med., 110 : 699-703, 1989.

A.195

THE CHOICE OF ECM RATE COULD IMPROVE THE NEUROPROTECTION DURING CPR

E.Iannuzzi, E.De Blasio, F.Ferraro, A.De Sio, F.Schiraldi
Cattedra di Anestesia e Rianimazione (dir. GF. Mostarda)
Medicina e Chirurgia II Ateneo Università di Napoli Italia

Introduction: Recent CPR guidelines (1) emphasize the importance of optimizing the external cardiac massage (ECM) rates in order to improve oxygen tissue delivery and acid product removal. We recently found that faster ECM rates improve cardiac output significantly but not $S\bar{v}O_2$ (2). Since the main aim of CPR is to maintain adequate coronary perfusion and cerebral blood flow (CBF),we investigated some metabolic/perfusional aspects of slower and faster MCE rates.

Methods: In 6 critically ill patients, needing CPR, a catheter was placed in the jugular bulb within the first minute of the circulatory arrest; the ECM was randomly performed in 3 patients at 80/m' for 3 m' followed by 130/m' for the next 3 m'; in the other 3 patients the sequence of ECM rates was inverted. At the end of each 3 m' period, samples of arterial, mixed venous and jugular venous blood were drawn for gas-analysis. The data collected were analysed using the T-Student test.

Results: Faster ECM rates were able to significantly improve $SjvO_2$, indipendent of the VSO_2 behaviour; besides the $\Delta CO_2a\text{-}jv$ at 130/m' was narrower than the $\Delta CO_2a\text{-}jv$ at 80/m' and than the $\Delta CO_2a\text{-}\bar{v}$ demonstrating a higher capacity of waste product removal.

ECM rates	130	80
SaO_2	84.2±20.4	78±25.3
$S\bar{v}O_2$	24.6±9	15.3±10.5
$SjvO_2$	36.1±11.2 ①	17.4±10.8
$\Delta Sa\text{-}\bar{v}O_2$	59.6±12.9	62.7±18.4
$\Delta Sa\text{-}jvO_2$	48.1±13	60.4±17.9
$\Delta CO_2\bar{v}\text{-}jv$	16.4±16.9	3.25±7.8
$PaCO_2$	47.2±20.9	45.3±20.2
$P\bar{v}CO_2$	83.4±35.9	88.3±34.5
PjO_2	67.0±27	85.1±37.7
$\Delta CO_2a\text{-}\bar{v}$	36.2±21.7	43±15.4
$\Delta CO_2a\text{-}jv$	19.8±8.3 ②	39.7±20.2
$\Delta SjvO_2$	11.5±3.4 ③	2.23±2.8
① $p<0.02$	② $p<0.05$	③ $p<0.001$

Conclusions: CPR with ECM rates >100/m' seems to improve C.O. and CBF allowing a better neuroprotection during the period of circulatory arrest.

References:1) Standards and guidelines on CPR and ECC. JAMA Oct, 28, 1992-vol.268,16. 2) Schiraldi F., et al.: Seeking the best ECM rate: which suggestions from CI and $S\bar{v}O_2$? Clin. Int. Care, sup. 3, 2:99,1992.

A.196

HELICOPTER TRANSPORTATION OF PATIENTS WITH SYMPTOMATIC AORTIC ANEURISMS

P. Felleiter, W. Breschinski, K. H. Bock

Dept. of Anaesthesiology and Intensive Care Medicine
Federal Armed Forces Hospital, Ulm, Germany

Background and goal of study. Helicopter transportation of patients with aortic aneurisms differs from most other interhospital transports. Therefore we investigated which specialties have to be expected, what kind of complications do arise and which measures can be taken to avoid them.

Methods. We retrospectively analyzed the patients transported with the Ulm-based rescue helicopter between March 1986 and February 1992. Data of 24 patients with symptomatic aortic aneurisms were taken from transport and helicopter protocols. Patients were divided into two groups, depending on whether the aneurism was ruptured or not. Complications were registered using a list of incidents liable to arise during the transportation of patients.

Results. In 42 % of the patients rupture of an aortic aneurism was diagnosed before the beginning of transportation. Systolic blood pressure was lower in patients with ruptured aneurisms ($p < 0.05$), less then 80 mm Hg were measured in 60 % of these patients at the beginning of transportation. These patients also received more infusion volume during the transportation ($p < 0.01$), but even combining volume replacement with the use of the medical anti shock trousers (70 %) and the application of positiv inotrope drugs (40 %) could not prevent that 44 % of these patients still had a systolic blood pressure of less then 80 mm Hg at the end of transportation. In the group of patients with non-ruptured aortic aneurisms, hypertension had to be treated in 50 % of the cases. In more than half of the patients with ruptured aortic aneurisms, accompanying physicians did see the necessity to place additional intravenous catheters (60 %) and/or to intensify the volume replacement therapy (70 %) before transportation could be started. No patient died during the transportation, complications did arise in two cases (8.3 %).

Conclusions. During secondary transportation of critically ill patients it is imperative to maintain the monitoring of vital functions, to continue the adequate therapy and to ensure that intervention by an accompanying physician is possible, when complications should arise. Transportation of patients with ruptured or non-ruptured aortic aneurisms requires great care in preparation as well as performance by both clinical and rescue teams. Treatment of hemorrhagic shock has priority for patients with ruptured aneurisms, whereas it is most important for patients with non-ruptured aneurisms to prevent rupture by careful handling and immediate treatment of hypertension.

A.197

THE PART OF RESCUE HELICOPTERS IN LARGE ACCIDENTS AND DISASTERS

Wenker Olivier
Medical Department, Swiss Air Rescue REGA,
Zürich, Switzerland

Background: Even if an helicopter is a multi-purpose flying machine, in the planning of rescue and disaster operations he is mostly only used as a transport facility for the injured. Nevertheless there were various functions that he could fulfill in the course of a rescue action at disasters as shown in the following

Mission possibilitys: *Search and supervision from the air:* Often there is some unclearness concerning the exact localization about the scene of accident. Air-search (as far as the weather allows it) is fast and effective. During the night may be used additionally special spotlight detectors. Beneath exact coordinates may also be transmitted to the operational base informations about the traffic density, additional dangerness and geographical qualitys of the accident place. This allows a better survey and therefore a more specific planning of the operational rescue work. *Staff and life-saving equipements:* Additional staff and special life-saving equipements can be delivered as fast as possible to the scene of accident. *Salvage operations:* In certain situations a helicopter lasts the only possibility of rescue. A cable-winch allows it either to set down a medical doctor and other staff at an impassable area or to rescue injured people carefully. There is also a big advantage in the search and rescue of shipwrecked persons and the evacuation of endangered persons from roofs during a fire. *Support of special rescue-troops:* Fire-fighters with special respiratory-support can be roped down on roofs. Divers can be brought fast to an accident-area in the water. At forest-fires some air-operated support for the extinguishing work may also be very helpful. At avalanche-accidents and landslips the discovery of buried persons can be pushed ahead by air-tranportation of special localizers and dog-teams. *Patient transport:* At larger accidents the optimal care of single patients inevitably brings up some difficulty. The evacuation of injured persons can be supported by air in the course of which should be aimed at a far-reaching evacuation. *Secundary transports:* Large-range transfers can help to avoid defiles at smaller hospitals. Carefull transports to specialized clinics can be exected and intensive care units can be relieved of postoperative patients.

Discussion: A rescue helicopter is a fast, mobile and versatile usable rescue auxiliary. Concerning larger accidents or disasters the initial functions, such as salvage operations, treatement and transport of single persons stay at least at the beginnig of a rescue operation in the background to enable other just shown assignements.

A.198

EVALUATION OF PAIN AND ANALGESIA IN A POSTANESTHESIA CARE UNIT

Frédéric Aubrun, Patrick Narchi, Dan Benhamou

Département d'Anesthésie, Hôpital Antoine Béclère,
Université Paris-Sud, 92141 Clamart, France

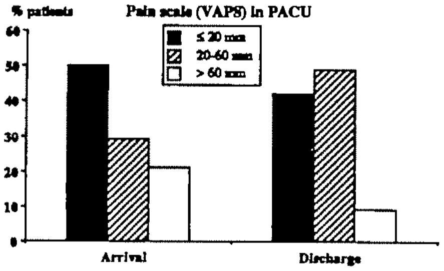
Background and goal of study: Systematic and early treatment of postoperative pain is more efficacious than on demand administration (1) and pretreatment with analgesics may result in decreased postoperative pain severity (2). The postanesthesia care unit (PACU) seems therefore the logical place where pain control should start.This study was thus intended to evaluate the degree of pain at arrival and during stay in PACU.

Material and methods: Pain was assessed in our PACU in 100 consecutive adults patients after orthopedic, abdominal or gynacologic surgery. Pain was evaluated by the same observer using a 0-100 mm visual analog pain scale (VAPS) 1) at arrival in the PACU and 2) immediately before patient's discharge from PACU. Pain was classified in 3 categories: minor (≤20), moderate (>20 and ≤ 60) and severe (> 60). PACU nurses were unaware of the VAPS results and used either a slow infusion of propacetamol intravenously (2g) or iv titrated morphine (2-3 mg every 10 min) according to the routine management of pain in our Department. The type of anesthesia (regional or general) and the analgesics administered during surgery were recorded, as well as the duration of stay in the PACU.

Results and discussion: Patients (mean age: 44 ± 17 y.o.) had been scheduled for orthopedic (21%), abdominal (34%), gynecologic (45%) surgery. Anesthesia was regional in 31% of cases. 50% and 58% of patients had moderate or severe pain at arrival and at discharge respectively (figure). 40% of our patients received propacetamol, 6% received iv morphine and 9% received a combination of both drugs. 33% of patients had a higher VAPS value at discharge than at arrival.

Conclusion: Pain was insufficiently treated in our PACU although 55% of patients received analgesics intravenously. A more precise and agressive pain control protocol is required.

References: 1 - Jørgensen BC, et al: Regular interval preventive pain relief compared with on demand treatment after hysterectomy. Pain 1985; 21:137-142.
2 - Katz J, et al: Preemptive analgesia: clinical evidence of neuroplasticity contributing to postoperative pain. Anesthesiology 1992; 77:439-446.



A.199

ORGANIZATION OF ACUTE PAIN SERVICES - A LOW-COST MODEL

Narinder Rawal

Department of Anaesthesia and Intensive Care, Örebro
Medical Center Hospital, Örebro, Sweden

Despite unprecedented interest in pain and its management, most patients undergoing surgery still receive treatments that have changed little in the past decades. The most common method of managing pain following surgery has been and still is the use of i.m. opioids prescribed on an "as needed" basis. The inadequacies of this method of pain management have long been recognized.

In the United States 24-hour acute pain services are being increasingly established to provide good quality analgesia. Such services usually consist of anesthesiologists, residents, specially trained nurses and pharmacists. The economic costs of such services are high ($200 or more per day per patient) and therefore the benefits not available to all surgical patients because of reimbursement regulations. Simpler and less expensive alternatives have to be developed if the aim is to improve the quality of postoperative analgesia for every patient on the surgical ward. Sophisticated analgesia techniques such as epidural and PCA are neither necessary nor realistic for most patients. Even in hospitals with well functioning acute pain services these techniques are used in less than 20% of all surgical patients.

Our nurse-based-anesthesiologist-supported model is based on the concept that postoperative pain relief can be greatly improved by provision of in-service training for nursing staff, optimal use of systemic opioids and peripherally acting analgesics and use of regional analgesia techniques in selected patients. Regular recording of pain intensity and treatment efficacy are the cornerstone of this model. Every patient who has undergone surgery is asked to grade his or her pain severity on VAS. This is done every 3 h and recorded on a specially reserved place on the bedside vital sign chart. Pain intensity is also scored before and 30-45 min after prescribed treatment. A VAS below 4 is aimed at all times.

A specially trained Acute Pain Nurse makes daily rounds of all surgery departments. Her duties include checking VAS recording on charts, helping with technical problems related to PCA or regional analgesia techniques and referral of problem patients to the anesthesiologist.

Appropriate guidelines regarding dose of analgesia, treatment of inadequate analgesia, patient monitoring, potential complications and their management are provided. Nurse responsibility and physician accountability are also defined. In the organization described above the only additional cost is that of the Acute Pain Nurse. At our hospital about 18000 surgical procedures are performed each year, all these patients can be expected to benefit from this low-cost organization.

A.200

EPIDURAL ADMINISTRATION OF LIPOSOMAL BUPIVACAINE FOR THE MANAGEMENT OF POSTSURGICAL PAIN.

Jean Boogaerts, Noelle Lafont, and Franz J. Legros.
Department of Anesthesiology and Intensive Care, Clinique Reine Fabiola, Montignies-sur-Sambre, Belgium.

Background and goal of study: Encapsulation of bupivacaine into multilamellar liposomes led to a reduction of systemic toxicity (1). Duration and quality of human postsurgical analgesia were compared between plain and liposomal bupivacaine after epidural injection.

Materials and Methods: Ten milliliters of sterile and apyrogenic solutions containing 0.5% bupivacaine, plain (BP; n=12) or encapsulated in multilamellar liposomes made of phosphatidylcholine and cholesterol in a molar ratio 4:3 (L-BP; n=14), were administereed to ASA Class I to III patients undergoing major surgery (abdominal, vascular, urologic, thoracic, orthopedic). One single dose injection was performed after completion of the operation through an epidural catheter inserted during the surgical procedure. The following parameters were measured: duration of analgesia, quality of motor blockade (Bromage scale) and sympathetic blockade (Hypotension). Data were expressed as Mean ± SEM. Significant differences were identified by Student's t test, ANOVA test and Mann-Whitney test.

Results and discussion:

	Analgesia (h)	Motor Block	Symp.Block
BP	3.2±0.4	9 patients	10 patients
L-BP	6.2±1.1*	0*	7 patients

* $p < 0.05$.

The duration of the analgesic action significantly increased from 3.2 to 6.2 hours. No motor block was observed.

Conclusion: The encapsulation of bupivacaine into multilamellar liposomes resulted in a prolongation of its postsurgical analgesic action without motor block.

Reference: 1. Boogaerts J, Declercq A, Lafont N et al. Toxicity of bupivacaine encapsulated into liposomes and injected intravenously. Comparison with plain solutions. Anesth Analg 1993; 75: in press.

A.201

POSTOPERATIVE ANALGESIA: A TWO DOSAGE REGIMENS TRIAL FOR I.M. MORPHINE AFTER EARLY I.V. TITRATION.

Karin Butscher, J.Xavier Mazoit, Kamran Samii

Anaes Dpt, Université Paris-Sud, Hôpital de Bicêtre,
94275 - Le Kremlin-Bicêtre, FRANCE

Background and goal of the study: The wide interindividual variability in analgesic needs often leads to therapeutic failure when opioids are administered systematically (1). The goal of this study was to evaluate the efficacy of two dosage regimens of i.m. morphine after an early i.v. titration in the postoperative period.

Methods: After ethical committee approval, 70 ASA I-II patients scheduled for abdominal, urologic or orthopedic surgery were randomly allocated into two groups. In the recovery room, when complaining, patients recieved morphine hydrochloride 3 mg i.v. every 10 min until satisfactory analgesia was achieved. If the total initial i.v. dose was ≥ 6 mg, analgesia was maintained with i.m. morphine. Group I received 2/3 of the initial i.v. dose 3 hours after the end of titration followed by 1/2 of the i.v. initial dose every 4 hours after. Group II received 1/2 of the initial i.v. dose 3 hours after the end of titration followed by 1/3 of the i.v. initial dose every 4 hours after. Pain was evaluated by visual analog scale, 0-10 cm (VAS). Statistics used semi-parametric analysis of repeated mesures. Data are mean ± SD.

Results and discussion: Twenty patients were excluded: 17 received paracetamol and codeine for maintenance after an initial i.v. dose ≤ 6 mg (n=17), one needed supplemental analgesia, two had sedation or respiratory depression in the recovery room. The total initial i.v. dose was 16.0 ± 6.5 mg (range 9-33 mg). Pain relief was similar in both groups during the first postoperative day (figure).

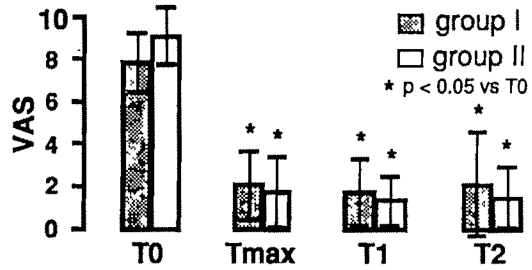


Figure: VAS at T0 = before i.v. titration, Tmax = end of i.v. titration, T1 = before the first i.m. injection, T2 = next morning.

Conclusion: Our study shows that an early titration of i.v.morphine in the postoperative period permits an efficient analgesia with a low dose i.m. maintenance regimen.

Reference:

1) Mitchell RW, Smith G: Br. J. Anaesth, 1989; 63: 147-158

A.202

ANALGESIA BY WOUND INFILTRATION BEFORE OR AFTER SURGERY IN INGUINAL HERNIORAPHY

Danielle Hennart, Yves Mersch
Department of Anesthesia, Erasme Hospital, Brussels, Belgium

Background and goal of study: Analgesia given before the painfull stimulus could prevent or reduce susbsequent pain. The aim of this study was to compare the effects of a neural blockade performed either before or after sugery.

Materials and methods: Fifteen male adults, ASA I or II, aged from 18 to 70 years, scheduled for inpatient unilateral inguinal herniorrhaphy were selected for the study after written informed consent. Midazolam 0.1 mg/kg IM was given for premedication. Anesthesia was induced with 2 mg/kg propofol and 0.02 mg/kg alfentanil. The patient's trachea was intubated after the injection of 0.5 mg/kg atracurium, and the lungs were mechanically ventilated with an O2/N2O mixture (FiO2: 0.4). Anesthesia was maintained by a continuous infusion of propofol (6 - 12 mg/kg/hour) and additional boluses of alfentanil (0.01 mg/kg) as needed. All patients had an infiltation of the abdominal wall along the line of the proposed incision 5 min. before surgery and an infiltration of the wound edges just before skin closure. Group A (N=7) received bupivacaine 0.5% before surgery and NaCl 0.9% at the end of surgery; group B (N=8) received NaCl 0.9% before and bupivacaine at the end of surgery. All infiltrations consisted of a volume of 0.25 ml/kg and were made in a double-blind manner. Morphine administered by a PCA pump was used for postoperative analgesia, allowing a precise assessment of the analgesic needs. Each bolus consisted of 2 mg, with a lock-out interval of 10 min and a maximal allowable dose of 20 mg in any 4 hours period. Pain was assessed using VAS at rest, during inspiration, and during cough, 12 hours and 24 hours after the end of surgery. Maximal inspiratory volume using incentive spirometry was measured the day before surgery, and 12 and 24 hours after surgery; patients were asked if maximal inspiration was limited by pain.

Results: Duration of surgery, and the amounts of propofol and alfentanil administered were statistically identical between the groups.

Group	Morph. at 12 H (mg)	Morph at 24 H (mg)	VAS rest 12H	VAS insp 12H	VAS cough 12H	VAS rest 24H	VAS insp 24H	VAS cough 24H
A	25±14	40±18	2 8±1.3	4 6±1.9	6 4±2 6	2.0±1.4	2 7±1.6	6.5±2 7
B	27±14	39±17	1.9±0 8	3.5±1.8	6 8±1.7	1 9±0 8	2 6±1.9	5.1±2 0

There was no statistical difference between the groups in any parameter exposed in the table, or in the maximal inspiratory volumes measured after surgery. Nevertheless, 24 H. after surgery, pain was not a subjective limiting factor in inspiration for any patient in Group A, but it remained a limiting factor for 4 patients in Group B (p=0.07, Fisher test).

Conclusions: Without reducing the amount of morphine needed, the preoperative infiltration with bupivacaine could have favorable effects on patients respiratory confort.

A.203

PREEMPTIVE ANALGESIA WITH EPIDURAL MORPHINE

Isabelle Nègre, Jean Pierre Guéneron, Samir Jamali,
Sylvaine Monin, Claude Ecoffey

Département d'Anesthésie-Réanimation
Université ParisSud, Hôpital de Bicêtre
94275 Le Kremlin Bicêtre Cedex, France

Background and goal of the study: Preemptive analgesia efficiently decreases postoperative pain (1). Therefore, we studied in a prospective double blind study the effect of pre-operative epidural morphine associated with general anaesthesia (GA) on intra- and post-operative pain intensity.

Material and methods: 20 ASA 1 or 2 patients, scheduled for major intra-abdominal surgery were randomized in 2 groups: Group I (n = 10) received lumbar subcutaneous injection of 3 ml 2% lidocaine with 1/200,000 epinephrine; Group II (n = 10) received an epidural injection at l3-l4 interspace of 5 mg preservative free morphine in 10 ml of 0.9% saline after a test dose of 2% lidocaine (3 ml) with 1/200,000 epinephrine. Thereafter, both group received GA with thiopentone, pancuronium and fentanyl 2 µg/kg. GA was maintained with isoflurane 1 MAC in O2 (40%)-N2O (60%). Fentanyl (2 µ/kg) reinjections were based on the following criteria: > 15 mmHg increase in systolic blood pressure, >15% increase in heart rate in absence of hypovolemia, expression of pain (sweat, tears, flushing). Post-operative pain relief was performed using morphine by PCA device (bolus demand dose: 1mg; lockout period: 10 min; no basal infusion rate). No other opiates or sedatives were administred. Pain score on a 10 cm visual analog scale (VAS) was recorded every 4 hours during 3 days. Intra- and post-operative analgesia was evaluated by means of: total amount of fentanyl used during anaesthesia, time between end of surgery and first demand of analgesia, total amount of iv morphine used during 3 days by periods of 12 hours, maximum score of VAS during the same periods. Side effects were noted.

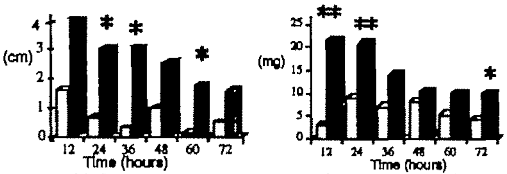
Results and discussion: Demographic data and duration of surgery were similar in both groups. Intra-operative use of fentanyl, post-operative needs of morphine for the 3 days and at 12 h, 24h and 72h were significantly lower in group II. Also, the pain score was significantly lower 24 h, 36 h, 60 h and 3 days after surgery. Delays between end of surgery were numerically higher in group II (see Table and figures). No serious complication was noted.

Conclusion: Single injection of 5 mg epidural morphine before major surgery has provided intra- and post-operative pain relief. During 3 days, patients needed very little amount of morphine almost during the first 12 hours allowing a soft recovery. Moreover, analgesia was more effective during 3 days.

	Fentanyl (mcg)	Total morphine (mg)	12 h morphine (mg)	Delay of first inj (min)
Group I	983 ± 682	85.7 ± 42.2	21.4 ± 13.8	232 ± 259
Group II	465 ±179*	36.9 ± 24.5**	3.1 ± 3.07**	480 ± 387

*p < 0.05, **p < 0.01 vs group I

□ Group I ■ Group II



VAS values   Morphine consumption

Reference: 1) Tverskoy et al. Anesth Analg 1990; 70: 29-35

A.204

ADDITION OF DROPERIDOL TO PCA MORPHINE: WHAT IS THE OPTIMAL DOSE?

C.T. Lamond, D.L. Robinson, J. T. Boyd,
J. N. Cashman

Department of Anaesthetics, St. Georges Hospital,
London, U.K.

Background and study aim: Patient Controlled Analgesia (PCA) is an increasingly popular method of providing effective and safe postoperative pain relief. However, there is a high incidence of nausea and vomiting (N&V) associated with iv PCA opioid administration, especially after gynaecological surgery. Although im promethazine (1) and transdermal hyoscine (2) can reduce the severity of N&V, the incidence remains unacceptably high. In contrast low dose iv droperidol (20 mcg/kg) is an effective antiemetic with few side effects. We have noted that N&V associated with iv opioid infusions, either continuous or PCA, can be reduced by the addition of droperidol to the infusate. This study was designed to find the optimal dose of droperidol to add to the PCA morphine infusate without increasing side effects.
Patients and methods: Ethics committee approval was obtained for a double blind, randomised, controlled study of healthy female patients (aged 18-65 yr) undergoing elective gynaecological surgery under general anaesthesia. Patients who had received preoperative opioid or antiemetic therapy were excluded. A standardised anaesthetic technique was used; premedication with temazepam 10-30 mg, induction with thiopentone 3-5 mg/kg and vecuronium 0.1 mg/kg followed by morphine 0.1-0.2mg/kg and isoflurane (<2%) in nitrous oxide and oxygen. Patients were randomised into one of 4 groups to receive morphine 1mg/ml plus droperidol either 0.05, 0.1, 0.15 or 0.2 mcg/ml via a Bard PCA pump delivering 1 ml bolus with a 5 min lockout period. Patients were allowed rescue medication of im metoclopramide 10 mg. PCA was commenced in recovery, with patients assessed every 15 min for the first hour, hourly for 4 hours and 4 hourly thereafter. N&V, sedation and pain were assessed using 5 point verbal rating scales. At the end of the 48 hour study period requirement for rescue antiemetic, occurence of neuroleptic side effects and patient satisfaction with therapy were recorded.
Results and discussion: In a pilot study droperidol 0.1 mcg/ml added to the PCA morphine infusate reduced the incidence of N&V from >60% to <10%. The effect of varying the dose of droperidol added to the PCA morphine infusate on N&V, sedation and the incidence of neuroleptic side effects will be presented.
Conclusion: Droperidol is an effective antiemetic when used with PCA morphine but at the expense of increasing sedation as dose increases.
References: (1) Silverman DG et al. Influence of promethazine on symptom-therapy scores for nausea during patient-controlled analgesia with morphine. Anesth Analg 1992:74:735-738. (2) Semple P et al. Transdermal hyoscine with patient-controlled analgesia. Anaesthesia 1992:47:399-401.

A.205

EFFECTS OF EPIDURAL CLONIDINE ON ANAESTHETIC REQUIREMENTS AND POSTOPERATIVE ANALGESIA

E. Samsó, G. Murga*, J. Valles, LL. Gallart, MM. Puig

Depts. of Anaesthesiology Hospital del Mar and Hospital de Figueres*, Autonomous University of Barcelona, Spain

Alpha$_2$ adrenergic agonists decrease intra and post-op analgesic requirements when administered transdermal, p.o., i.v.or i.m. The aim of the present study was to determine the effects of a single dose of epidural clonidine on anaesthetic requirements and post-op analgesia during epi-general anaesthesia.
Methods. Sixty ASA I-II patients scheduled for total abdominal hysterectomy were randomly distributed into groups:

GROUP	GEN ANAESTH(GA)+ EPIDURAL(EP)		
I	ISOFLURANE(IS)	+	SALINE(SS)
II	ISOFLURANE	+	CLONIDINE(CL)
III	FENTANYL(FE)	+	SALINE
IV	FENTANYL	+	CLONIDINE

Institutional and individual informed consents were obtained. After placement of an EP catheter, GA was induced with atropine, midazolam, thiopental and vecuronium. At this time, all patients received 15 ml of EP SS with or without clonidine (300 ug). Surgical anaesthesia was maintained with 60% N2O in O2, plus IS or FE administered at the doses required to keep BP and HR within 20% of baseline values. Groups III and IV also had a constant infusion of midazolam (0.75 ug/kg/min). Results are expressed as % expired IS (weighted mean of the overall concentrations obtained by mass spectrometry), and mean dose of FE in ug/kg/h.
Results: All groups were similar in respect to age, BMI, MAP, HR and duration of surgery. Anaesthetic requirements and time of request of post-op analgesia (AR) are shown in the Table.

GROUP	% IS	FE(ug/kg/h)	AR(min)
I	0.51±0.03	—	57±6
II	0.17±0.02**	—	130±18**
III	—	3.4±0.4	72±31
IV	—	2.0±0.1*	235±33**

mean ± SEM; *$p<0.05$ and **$p<0.01$

Conclusions. EP clonidine: a) decreases intra-operative FE and IS requirements and b) increases AR time, demonstrating significant post-operative analgesia.

A.206

SAFETY OF PCA IN ELDERLY

E.Santangelo*, B.Amantea*, A.Sansone,
G.Savoia, B.Sparacia

Department of Anaesthesia and Intensive Care
Catanzaro* and Palermo Medical Schools, Italy.

Background and goal of study: The goal of our study was to demonstrate the safety of PCA in patients older than 65 years, in order to verify absence of major desaturations or great alterations of respiratory patterns. We have compared ketorolac, morphine and buprenorphine PCA in 3 groups of 20 elderly.

Materials and methods: 60 patients older than 65 years submitted to median laparotomy, anaesthetized with standard balanced tecnique (propofol 1,5-2 mg/kg, isoflurane 1,3 MAC, fentanyl 1,5-3 mcg/kg, atracurium 500mcg/kg) were treated with PCA in the first 24 postoperative hours. PCA details are showed in tab.I.

Tab.I: PCA details

	Group A(20) ketorolac mg	Group B(20) morphine mg	Group C(20) buprenor.mcg
initial bolus	9	3	90
bolus dose	3	1	30
continuous infusion hourly	1,5	0,5	15
max 24h	180	60	1000
lockout time	15'	15'	15'

We have evaluated 24 hours consumption, VAS integrated score(Σ of hourly VAS 0-10 cm- 0-240 values), the number of patients with pain relief of 50% in the first 4 hours, number of patients with sedation score (0-4 points)>2, number of patients >3 major desaturations (SaO2%<85%, >30''), incidence of nausea and vomiting and minimental status evaluation at 24 hours.

Results and discussion: As showed in tab.II, collateral effects are minimal and easily controllable; better quality of analgesia was achieved with buprenorphine; safety, but not better analgesia was found using ketorolac.

Tab.II: Results

	Group A ketorolac mg	Group B morphine mg	Group C bupreno.mcg
24h consumption	75(57-127)	18(12-26)	550(400-700)
VAS integrated score	80(42-123)	72(36-110)	65(30-106)
n° of pt with 1/2 VAS in the first 24h	7/20	10/20	14/20
sedation score > 2	0/20	3/20	4/20
n° of pt with plus than 3 major desaturation	0/20	4/20	3/20
nausea/vomiting	7/5	8/6	6/5
24h minimental status range	20-24	16-22	18-23

Conclusion: Postoperative pain control with PCA in elderly is safe, even if further studies are necessary to improve quality of analgesia and to find better drugs associations.

A.207

POSTOPERATIVE HYPOXAEMIA : COMPARISON OF EPIDURAL AND PATIENT CONTROLLED ANALGESIA

Amanda Spencer, Fayezi Farhat, Jean-Louis Bourgain,
Christian Jayr

Department of anesthesiology, Institut Gustave Roussy,
Villejuif, France

Background and goal of study : It has been previously demonstrated that postoperative extradural opioid analgesia tended to cause longer periods of postoperative hypoxaemia than parenteral opioid analgesia (1). The aim of this study was to examine the effect on postoperative arterial oxygenation hemoglobin saturation (SaO2) of two different analgesia regimens ; epidural and patient controlled-analgesia after abdominal surgery for cancer.

Materials and methods : Twenty patients scheduled for abdominal surgery for cancer gave informed consent to this study. The group EPI received postoperatively epidural bupivacaine 0.125% (50 mg/4h) and morphine (1 mg/4h) - The group PCA received postoperatively self adminestered IV morphine at a maximum rate of 1 mg every 5 min using patient controlled- analgesia system. All patients received etomidate, fentanyl, vecuronium, isoflurane and O2/N2O general anesthesia. Arterial oxygen saturation was monitored continuously during the preoperative night and for 24 hours after operation, while the patient breathed air, using a Nellcor N-200 pulse oximeter interfaced with a microcomputer. Recordings of SaO2 were made every 10 seconds and stored by the computer. The percentage of time spent with SaO2 between 95% and 90%, 90% and 85% and less than 85% was analysed for the two groups and individual patients. Pain scores were obtained after operation using a 0-10 cm visual analogue scale. For statistical analysis between groups, analysis of variance with repeated measures was used.

Results : Patients in the EPI and PCA groups were not statistically different with respect to age, sex, preop SaO2. In the EPI group the pain relief was significantly better. Results of SaO2 are in the table.

Conclusion : Postoperative hypoxaemia occured in both analgesia groups but no statistical difference was found between the two groups. Epidural morphine associated with local anesthetic did not tend to cause longer episods of postoperative hypoxaemia compared with these of patient-controlled morphine analgesia group.

SaO2	EPI Group n = 10	PCA Group n = 10
Pre-op.		
<95%	20 (15)	25 (16)
Postop.		
<95%	48 (15)	55 (16)
<90%	20 (10)	15 (8)
<85%	2 (4)	2 (3)

Duration of hypoxaemia (percentage of time). Values are means (SD).

Reference : Wheatley RG et al. Br J Anaesth 1990;64:267-275.

A.208

PHARMACOKINETICS OF INTRANASAL FENTANYL

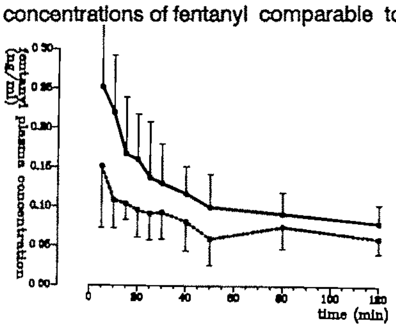
*Striebel H. Walter, **Krämer Joachim, ***Luhmann Ingeborg, ***Rohierse-Hohler Ingrid, *Tritsch Andreas

*Department of Anaesthesiology and Intensive Care Medicine, Steglitz Medical Center, Free University of Berlin, FRG
**Department of Anaesthesiology, Urban Hospital, Berlin, FRG
***Janssen Research Foundation, Neuss, FRG

Background and goal of study: We recently demonstrated that fentanyl titration can be adjusted to individual requirements by intranasal administration (1). To date there exists no pharmacokinetic data about intranasal fentanyl.

Materials and methods: The study was approved by the local ethics committee. In a randomized, double-blind cross-over study, 8 volunteers received either 12 premetered puffs (0.054 mg) of fentanyl intranasally and simultaneously 12 ml NaCl 0.9% intravenously, or 12 puffs of NaCl 0.9% intranasally and 12 ml of a diluted fentanyl solution (0.054 mg) intravenously. There was a time lag of at least 7 days between the two pharmacokinetic studies. Venous blood was sampled from a cubital vein at 5, 10, 15, 20, 25, 30, 40, 50, 80 and 120 min after dosing. C_{max}, t_{max}, AUC $t_0 - t_\infty$ and bioavailability were calculated.

Results and discussion: Median values: C_{max} (ng/ml) nasal: 0.16, i.v.: 0.26; t_{max} (min) nasal: 10, i.v. 5; AUC $t_0 - t_\infty$ (min · ng/ml) nasal: 14.6, i.v. 22.0; bioavailability (%) nasal: 76.6. Intranasal fentanyl (---) administration provides a rapid rise in plasma concentrations of fentanyl comparable to i.v. (——) administration (Fig.). The bioavailability of 76.6% is rather high and comparable to those of intranasal sufentanil (2).



Conclusion: Intranasal fentanyl is characterized by rapid resorption and a high bioavailability.

References: 1. Striebel HW et al. Anesthesiology 1992; 77: 281 - 285 2. Helmers JHJH et al. Can. J. Anaesth. 1989; 36: 494 - 497

A.209

INTRANASAL FENTANYL FOR POSTOPERATIVE PAIN MANAGEMENT IN AN UNSELECTED POPULATION

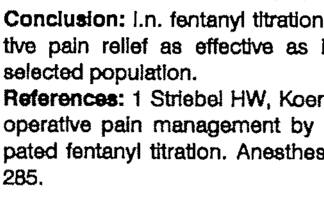
Walter H. Striebel, Jens Pommerening,
Armin Rieger, Glenda Brummer

Department of Anaesthesiology and Operative Intensive Care Medicine, Steglitz Medical Center, Free University of Berlin, FRG

Background and goal of study: In patients undergoing surgery for lumbar disc protrusion, intranasal (i.n.) fentanyl provides a pain relieving effect comparable to intravenous (i.v.) fentanyl (1). The aim of the study was to investigate whether i.n. fentanyl is suitable for postoperative pain management under routine conditions (different types of premedication, surgery and anesthesia).

Materials and methods: After approval by the local ethics committee and written consent 112 patients (ASA I,II,III) were included in this study. For postoperative pain relief patients received either 0.027 mg fentanyl i.n. and NaCl 0.9% i.v. (i.n. group, n = 53) or NaCl 0.9% i.n. and 0.027 mg fentanyl i.v. (i.v. group, n = 59). These doses were repeated every 5 min. until the patients were free of pain or refused further analgesia. Subjective pain intensity was evaluated with a numerical rating scale (0 = no pain; 100 = worst pain possible) before beginning opioid titration and 5, 10, 15, 20, 30, 40, 50, 60, 70 and 80 min. thereafter.

Results and discussion: The two groups were not statistically different with respect to age, weight, height, duration of surgery and anesthesia. The patients in the i.v. group required 0.099 ± 0.06 mg fentanyl versus 0.106 ± 0.06 mg in the i.n. group (n.s.). Subjective pain intensity decreased significantly within 5 min. in the i.v. (——) as well as in the i.n. (---) group (Wilcoxon-test for matched pairs) (Fig.; median and interquartile range). Only at the 15-min. measurement point was pain intensity significantly lower in the i.v. group (Mann-Whitney U-test). No patient required naloxone.



Conclusion: I.n. fentanyl titration provides a postoperative pain relief as effective as i.v. fentanyl in an unselected population.

References: 1 Striebel HW, Koenigs D, Krämer J: Postoperative pain management by intranasal demand-adapted fentanyl titration. Anesthesiology 1992; 77: 281 - 285.

A.210

INTRANASAL FENTANYL FOR BREAKTHROUGH CANCER PAIN OR INCIDENT PAIN

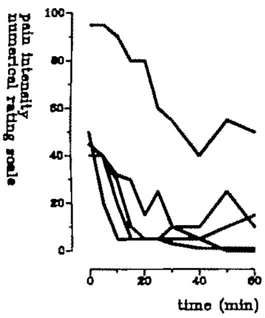
Walter H. Striebel, Anne Wessel, Armin Rieger,
Natalie Boerger

Department of Anaesthesiology and Operative Intensive
Care Medicine, Steglitz Medical Center,
Free University of Berlin, FRG

Background and goal of study: A high percentage of patients with chronic malignant pain transitory experience breakthrough cancer pain or incident pain. For "rescue" medication a fast acting and powerful analgesic should be available to the patient (1). Recent studies have shown, that intranasal (i.n.) fentanyl meet these criteria (2).

Materials and methods: The aim of this pilot study was to investigate the suitability of demand-adapted, i.n. fentanyl administration for breakthrough cancer pain or incident pain. The study was approved by the local ethics committee. Written consent was given by 5 patients. When experiencing acute worsening of pain, i.n. fentanyl (0.027 mg) via a spray bottle with a premetered spray was administered. This fentanyl dosage was repeated in 5 minute intervals until the patients experienced marked pain relief. Subjective pain intensity was assessed with a numerical rating scale (0=no pain, 100=worst pain possible).

Results and discussion: During the study period the 5 patients received a total of 0.189 mg, 0.108 mg, 0.162 mg, 0.054, 0.216 mg of fentanyl. Rapid onset and marked reduction of pain intensity was achieved in all patients (Fig.). All patients rated the pain relief as good or very good. Pain in the nose was not reported.



Conclusion: This open study shows that i.n. fentanyl provides fast acting, efficacious and non invasive pain reduction in patients with breakthrough cancer pain or incident pain. Further studies are warranted.

Reference: 1 Portenoy RK et al. Pain 41 (1990) 273 - 281. 2 Striebel HW et al. Anesthesiology 1992; 77: 281 - 285

A.211

TREATMENT OF CANCER PAIN WITH MORPHINE (MO) - A DOUBLE BLIND STUDY OF EXTRADURAL (ED) VERSUS INTRAMUSCULAR (im) ROUTES OF ADMINISTRATION.

Sherdil Nath and Gunnel Ehrenström Reiz.

From the Department of Anaesthesiology, University of Umeå, Umeå, Sweden.

Background and goal of study: ED administration of MO or other opioids is a well established technique for treatment of cancer pain. Despite its wide-spread use, controlled data of its efficacy in relation to the type of pain are lacking. One uncontrolled study (1) and much clinical experience do, however, indicate that ED MO has little or no effect in neurogenic pain. The aim of this study was to compare the efficacy of extradurally administered MO on terminal cancer pain using a classical double-blind, partly cross-over design with im MO as the control.

Patients and methods: Forty patients with severe, terminal cancer pain and unsatisfactory response to oral or parenteral analgesics were incuded in the study after institutional approval and informed consent. A malignant focus of pain was always identified. The type of pain was described as musculo-skeletal (MS), visceral (V), neurogenic (N) or any combination thereof. Patients were randomized to receive either ED MO, 4 mg in 10 ml normal saline (NS) given 6 hourly along with an im injection of 1 ml NS, or 10 mg (1ml) MO im along with 10 ml of ED NS at the same intervals. The double-blind regimen was maintained for 72 h and visual analogue scores (0-10) obtained 1 hour after each dose. Additional analgesics (pethidine or ketobemidone) were given im as needed. After 72 h, patients who had received im MO were switched to ED MO, individually dosed, for another 72 h and patients given ED MO had their dose adjusted if required.

Results and discussion: The im group comprised 20 patients with 11 components of N, 7 of MS and 6 of V pain. Therapy was regarded as satisfactory in 2 N, 1 MS and 1 V pain. In the ED group, comprising 20 patients with 8 N, 11 MS and 4 V pains, therapy was satisfactory in 7 MS ($p<0.05$ compared to im MO), 2 V and 0 N pains. Less suplementary analgesics were required in the ED group. Of the poor responders in the im group, 2 MS and 2 V, but none of the N pains responded satisfactorily when given ED MO in an open, individually dosed fashion. When the ED MO patients had their dose adjusted after termination of the double-blind period, MS and V but not N pains could be well controlled. It is concluded that ED MO is more effective than im MO in the treatment of musculo-skeletal cancer pain but that neither of these are effective in neurogenic pain. Visceral pain can sometimes be controlled with ED MO at higher doses.

Reference: 1. Arnér S & Arnér B: Acta Anaesthesiol Scand 1985, 29:32.

A.212

HIGH DOSE ORAL MORPHINE IN CANCER PAIN MANAGEMENT

Lukas Radbruch, Stefan Grond, Detlev Zech, Klaus A. Lehmann

Department of Anaesthesiology, University of Cologne, Cologne, Germany

Background and goal of study: Due to differences in pain type, tumor spread and individual bioavailability efficient doses of oral morphine have a wide range. Though its use in cancer pain has been thoroughly investigated, little has been published on the high dose range. In this retrospective study, efficacy and side effects of high dose oral morphine were evaluated.

Materials and methods: From 1983-1991, 705 patients (males 379, females 326, 58±12 years) with advanced cancer were treated in our pain clinic with oral morphine (solution or sustained-release tablets). 111 of these patients received 200-599 mg/d, and 14 patients 600-2400 mg/d. Pain intensity (verbal rating scale) and side effects were assessed regularly.

Results and discussion: Patients were treated on 36823 days with oral morphine. According to WHO-guidelines morphine was combined with nonopioid analgesics on 96% of treatment days and with adjuvant drugs (laxatives 68%, antiemetics 46%, hypnotics 45%, antipsychotics 21%, antidepressants 21%, anticonvulsants 20%, steroids 17%) on 97% of days. No serious adverse events, such as respiratory depression or allergic reaction, were observed.

Table: Pain intensity and symptoms during treatment with oral morphine

morphine (mg/d)	<200	200-599	≥600
days (n)	30626	5198	999
Pain intensity			
none-moderate	86%	78%	67%
severe-maximal	10%	13%	33%
no assessment	4%	9%	0%
Symptoms			
Dyspnoea	15%	7%	41%
Dysphagia	17%	18%	36%
Constipation	26%	32%	31%
Nausea	26%	23%	23%
Insomnia	23%	25%	22%
Neurol.-psych. symp.	25%	28%	21%
Anorexia	26%	28%	18%
Hyperhidrosis	13%	14%	12%
Dyspepsia	7%	7%	10%
Urinary symptoms	16%	20%	6%
Diarrhea	8%	3%	4%
Vomiting	16%	15%	3%
Pruritus	8%	6%	0%

Conclusion: Oral morphine is a safe analgesic drug even in the high dose range. Severe pain, dysphagia and dyspnoea were seen more frequently in patients with morphine doses ≥600 mg/d, representing far advanced cancer disease in these patients. Side effects of morphine therapy were not increased in this group, due to symptomatic treatment with adjuvant drugs.

A.213

INTRATHECAL PAIN RELIEF IN TERMINALLY ILL CANCER PATIENTS AT HOME.

Wagemans MFM, Zuurmond WWA, Spoelder EM, Lange JJ de.

Department of Anesthesiology, Academic Hospital Vrije Universiteit, PO BOX 7057, Amsterdam.

Forty patients with cancer pain in the terminal phase, who had either insufficient pain relief with high doses of morphine or severe side effects from systemic analgesics were selected for continuous administration of morphine. An intrathecal catheter was implanted, tunnelled and connected with a portable infusion pump, delivering morphine constantly and if needed on demand. The proper dose was titrated and after stabilization, patients were discharged from the hospital if adequate home care could be guaranteed. During hospitalization and at home, daily doses of morphine, concomitant medication, pain scores measured with help of the Visual Analogue Scale (VAS) and activities were meticulously registered in patient's pain diary. The total number of catheter days was 1486, of which 1009 were spent at home. Patients were treated for a mean of 37.2 (range 2 - 183) days.

Sufficient pain relief (a VAS score < 5) was achieved in 37 patients (92.5 %). Meningitis occurred in 2 patients, however the early detection of this complication resulted in adequate treatment with antibiotics. The catheter could be re-instilled within 10 days. Minor complications like postspinal headache and withdrawal symptoms, occurred mostly during the stabilization phase. The catheter was removed inadvertently 6 times and could be replaced on outpatient basis. In terminally ill cancer patients, the continuous intrathecal , administration of morphine may be recommended if conventional pain relief fails.

AUTHOR INDEX

Abels, R. *see* Faris, P. P., (*ESA*) A.101
Aderjan, R. *see* Motsch, J., (*ESA*) A.155
Aitkenhead, A. R. *see* Mahajan, R. P., (*ESA*) A.68
Åkeson, J., Björkman, S. and Messeter, K. Midazolam prevents ketamine-induced stimulation of cerebral metabolism, (*ESA*) A.111
Albanese, J., Viviand, X., Durbec, O., Alliez, B. and Martin, C. Sufentanil increases intracranial pressure in patients with head trauma, (*ESA*) A.107
Alfonsi, P., Hongnat, J.-M., Lebrault, C. and Chauvin, M. Fentanyl, as pethidine, inhibits post anaesthesia shivering, (*ESA*) A.74
Ali-Melkkilä, T., Virkkilä, M., Soini, H. and Kanto, J. Pharmacokinetics and effects of i.m. alfentanil as premedication for outpatient cataract surgery, (*ESA*) A.145
Alliez, B. *see* Albanese, J., (*ESA*) A.107
Allsop, E. *see* Innes, P., (*ESA*) A.167
Alon, E., Lenzlinger, P. M. and Pasch, T. Ondansetron 4 mg *vs* droperidol 1.25 mg in the prophylaxis of postoperative nausea and vomiting after alfentanil-supplemented inhalation anaesthesia, (*ESA*) A.12
Alon, E. *see* Biro, P., (*ESA*) A.156
Alvarez, J., Camara, M. L., Cortiñas, J., Cortes, J. and Aris, A. Pulmonary and systemic vascular effects of isoproterenol, nitroglycerin and prostaglandin E1 early after cardiac operations in patients with pulmonary hypertension, (*ESA*) A.27
Amantea, B. *see* Santangelo, E., (*ESA*) A.206
Amery, A. *see* Wiebalck, A., (*ESA*) A.90; (*ESA*) A.154
Anderson, J. *see* Carli, F., (*ESA*) A.86
Ariès, J. *see* Arné, J., (*ESA*) A.1
Aris, A. *see* Alvarez, J., (*ESA*) A.27
Armellin, G., Sorbara, C., Pittarello, D., Penzo, D. and Giron, G. P. Acute preoperative plasmapheresis during cardiac surgery, (*ESA*) A.104
Arné, J., Descoins, P., Bresard, D., Ariès, J. and Fusciardi, J. A new clinical score to predict difficult intubation, (*ESA*) A.1
Arock, M. *see* Riou, B., (*ESA*) A.103
Arroyo, J. L. *see* Catalá, J. C., (*ESA*) A.89; De los Ríos, J., (*ESA*) A.75; Monedero, P., (*ESA*) A.98
Arthaud, M. *see* Bodin, L., (*ESA*) A.191
Aubert, M. *see* Kozak Ribbens, G., (*ESA*) A.92
Aubrun, F., Narchi, P. and Benhamou, D. Evaluation of pain and analgesia in a postanesthesia care unit, (*ESA*) A.198
Auffray, J.-P. *see* Martin, C., (*ESA*) A.190
Auroy, Y., Gillon, M.-C., Bismuth, H. and Ecoffey, C. Measurement of sigmoid intramural pH during orthotopic liver transplantation, (*ESA*) A.76
Auroy, Y. *see* Descraques, C., (*ESA*) A.127
Aya, G. *see* Lefrant, J. Y., (*ESA*) A.18

Babik, B. *see* Vereczkey, Z., (*ESA*) A.64
Bach, A. *see* Motsch, J., (*ESA*) A.155
Backman, C. *see* Hohner, P., (*ESA*) A.41
Baconnier, P. *see* Py, C., (*ESA*) A.57
Bailey, C. R., Ruggier, R. and Findley, I. L. Diamorphine/bupivacaine mixture *vs* plain bupivacaine: a comparison of epidural infusions in labour, (*ESA*) A.169
Balatoni, E. *see* Zaouk, G., (*ESA*) A.11
Bålfors, E. and Franklin, K. Cerebral perfusion during obstructive sleep apnea (OSA), (*ESA*) A.62
Bålfors, E. *see* Svanström, M., (*ESA*) A.177
Baller, S. *see* Motsch, J., (*ESA*) A.155
Baltás, B. *see* Vereczkey, Z., (*ESA*) A.64
Banssillon, V. *see* Py, C., (*ESA*) A.57
Bardoczky, G., Engelman, E. and d'Hollander, A. Continuous spirometry: an aid in the intraoperative respiratory monitoring—case reports, (*ESA*) A.55
Bardoczky, G. *see* Engelman, E., (*ESA*) A.56
Baron, J.-F. *see* Delayance, S., (*ESA*) A.45; Fellahi, J. L., (*ESA*) A.44
Barré, J. *see* Plaud, B., (*ESA*) A.141
Baudot, J., Vertommen, J. D. and Van Aken, H. Patient controlled epidural analgesia *vs* intermittent injections during labor using 0.125% bupivacaine and sufentanil, (*ESA*) A.170
Baurain, M. J., Dernovoi, B. S., d'Hollander, A. A. and Bollen, P. C. Reversal of vecuronium induced neuromuscular blockade: No effects of atropine administration timing, (*ESA*) A.134
Baurain, M. J., Dernovoi, B. S., d'Hollander, A. A. and Schmartz, D. M. Can repetition of high frequencies stimuli alter the value of 50 and 100 Hz tetanic fade during vecuronium induced neuromuscular blockade? (*ESA*) A.135; Comparison between double-burst stimulation and 50, 100 Hz tetanic fade during spontaneous recovery of vecuronium induced neuromuscular blockade, (*ESA*) A.133
Baurain, M. J. *see* Dernovoi, B. S., (*ESA*) A.137
Bayhan, N., Güzeldemir, M. E. and Türkan, H. The effects of bupivacaine, mepivacaine and prilocaine on platelet aggregation, (*ESA*) A.123
Bazin, J. E., Gillart, T., Comte, A., Dubray, C. and Schoeffler, P. Does nicardipine potentiate the neuromuscular block of atracurium? (*ESA*) A.136
Beaussier, M., Coriat, P., Gosgnach, M., Portilla, M., Kalfon, P. and Viars, P. Determinants of systolic pressure variation in patients ventilated after vascular surgery, (*ESA*) A.37
Beaussier, M. *see* Gosgnach, M., (*ESA*) A.21
Bedrossian, J. *see* Jacob, L., (*ESA*) A.85
Begon, C. *see* Jamali, S., (*ESA*) A.160
Ben Ameur, M. *see* Reignier, J., (*ESA*) A.162
Benhamou, D., Malinowsky, J.-M., Quinquis, V., Bourget, P. and Couarraze, G. Slow-release effect of pH-adjusted bupivacaine: pharmacokinetic demonstration, (*ESA*) A.120
Benhamou, D. *see* Aubrun, F., (*ESA*) A.198; Hamza, J., (*ESA*) A.171; Joly, L.-M., (*ESA*) A.58
Bennet, J., Ramachandra, V. and Carli, F. An investigation into the effect of passive and active cutaneous warming devices on intraoperative body temperature in elderly patients, (*ESA*) A.73
Bennett, S., Nelson, V. and Green, T. Propofol (2,6 diisopropylphenol) as an antioxidant *in-vitro*: a dose response study, (*ESA*) A.152
Bernaus, M. *see* Fernandez, D., (*ESA*) A.131
Bernière, J. *see* Murat, I., (*ESA*) A.165
Bertrand, M. *see* Gosgnach, M., (*ESA*) A.5; (*ESA*) A.6
Bertrix, L. *see* Freysz, M., (*ESA*) A.46
Beydon, L., Rauss, A., Lofaso, F., Harf, A. and Bonnet, F. A survey of sleep problems in surgical patients, (*ESA*) A.4
Beydon, L. *see* Catoire, P., (*ESA*) A.192; Liu, N., (*ESA*) A.128; Mimoz, O., (*ESA*) A.180
Biber, B. *see* Raner, C., (*ESA*) A.49; Sundeman, H., (*ESA*) A.50
Binning, A. *see* Forbes, D., (*ESA*) A.125
Biro, P., Alon, E., Weidmann, G. and Pietzsch, S. Dose dependent effects of oral medication with midazolam, (*ESA*) A.156
Bismuth, H. *see* Auroy, Y., (*ESA*) A.76
Bitker, M. *see* Mouquet, C., (*ESA*) A.83
Bitker, M.-O. *see* Mouquet, C., (*ESA*) A.82; (*ESA*) A.84
Björkman, S. *see* Åkeson, J., (*ESA*) A.111
Blin, O. *see* Paut, O., (*ESA*) A.10
Blockmans, D., Van Hemelrijck, J. and Van Aken, H. Ketamine does not prevent hypotension caused by induction of anaesthesia with propofol in elderly patients, (*ESA*) A.40
Bock, K. H. *see* Felleiter, P., (*ESA*) A.196
Bodin, L., Laurent, P., Do-Khac, T., Zouaoui, Z., Lamas, G., Cambau, E., Rouby, J. J. and Viars, P. Incidence of bacterial maxillary sinusitis in critically ill patients with radiologic maxillary sinusitis, (*ESA*) A.179
Bodin, L., Maghrebi, H., Kaddour, C., Arthaud, M., Rouby, J. J. and Viars, P. Non invasive monitoring of CO_2 in patients with septic shock, (*ESA*) A.191
Bodin, L. *see* Rouby, J. J., (*ESA*) A.181

Boer, F., Engbers, F., Burm, T., Bovill, J. and Hak, A. Sufentanil first-pass pulmonary uptake at three different steady state concentrations of the drug, (*ESA*) A.147
Boerger, N. *see* Striebel, W. H., (*ESA*) A.210
Böhrer, H. *see* Geiger, C., (*ESA*) A.14
Bollen, P. C. *see* Baurain, M. J., (*ESA*) A.134; Dernovoi, B. S., (*ESA*) A.137
Bonara, Z. *see* Foppoli, R, (*ESA*) A.132
Bonneau, M. *see* Samama, C. M., (*ESA*) A.100
Bonnet, F. *see* Beydon, L., (*ESA*) A.4; Catoire, P., (*ESA*) A.192; Fulgencio, J. P., (*ESA*) A.42; Liu, N., (*ESA*) A.25; (*ESA*) A.128; Mimoz, O., (*ESA*) A.180
Bonnin, P. *see* Samama, C. M., (*ESA*) A.100
Boogaerts, J., Lafont, N. and Legros, F. J. Epidural administration of liposomal bupivacaine for the management of postsurgical pain, (*ESA*) A.200
Boogaerts, J. *see* Legros, F. J., (*ESA*) A.122
Booker, P. *see* Innes, P., (*ESA*) A.167
Boosaert, L. *see* Heytens, L., (*ESA*) A.178
Borissov, B. *see* Smilov, I., (*ESA*) A.176
Borsarelli, J. *see* Kozak Ribbens, G., (*ESA*) A.92
Böttiger, B. *see* Rauch, H., (*ESA*) A.30
Bougnières, P. *see* Menigaux, C., (*ESA*) A.175
Bouillon, R. *see* Wiebalck, A., (*ESA*) A.90; (*ESA*) A.154
Bourgain, J. L. *see* Lequeau, F., (*ESA*) A.97
Bourgain, J.-L. *see* Spencer, A., (*ESA*) A.207
Bourget, P. *see* Benhamou, D., (*ESA*) A.120
Bovill, J. *see* Boer, F., (*ESA*) A.147
Boyd, J. T. *see* Lamond, C. T., (*ESA*) A.204
Brandom, B. W. *see* Meretoja, O. A., (*ESA*) A.140
Bredenkötter, U. *see* Schregel, W., (*ESA*) A.105
Bresard, D. *see* Arné, J., (*ESA*) A.1
Breschinski, W. *see* Felleiter, P., (*ESA*) A.196
Bromberg, N., Decoene, C., Chammas, E., Pol, A. and Krivosic-Horber, R. Echocardiographic study of the induction with a low-dose of sufentanil for coronary artery surgery, (*ESA*) A.28
Browne, D. *see* Mythen, M., (*ESA*) A.29
Bruelle, P. *see* de La Coussaye, J. E., (*ESA*) A.121
Brummer, G. *see* Striebel, W. H., (*ESA*) A.209
Bruneval, P. *see* Samama, C. M., (*ESA*) A.100
Brutsaert, D. L. *see* De Hert, S. G., (*ESA*) A.47
Burm, T. *see* Boer, F., (*ESA*) A.147
Butscher, K., Mazoit, J. X. and Samii, K. Postoperative analgesia: a two dosage regimens trial for i.m. morphine after early i.v. titration, (*ESA*) A.201

Caen, J. P. *see* Samama, C. M., (*ESA*) A.100
Calappi, E. *see* Mulazzi, D., (*ESA*) A.54
Calmatte, S. *see* Orliaguet, G., (*ESA*) A.163
Camara, M. L. *see* Alvarez, J., (*ESA*) A.27
Camarero, A. *see* Martínez Urionabarrenetxea, K., (*ESA*) A.187; Pérez Arancón, J. L., (*ESA*) A.188
Cambau, E. *see* Bodin, L., (*ESA*) A.179
Camboulives, J. *see* Paut, O., (*ESA*) A.10
Camus, Y., Delva, E. and Lienhart, A. Preoperative skin-surface warming reduces intraoperative hypothermia, (*ESA*) A.72
Carayon, A. *see* Mouquet, C., (*ESA*) A.83; (*ESA*) A.84
Carli, F., Anderson, J., Read, M. and Halliday, D. Effect of recombinant human growth hormone (HGH) on protein metabolism in surgical patients, (*ESA*) A.86
Carli, F. *see* Bennet, J., (*ESA*) A.73; Kulkarni, P., (*ESA*) A.70
Carrascosa, F. *see* Hidalgo, F., (*ESA*) A.99; Monedero, P., (*ESA*) A.98
Carrera, J., Monedero, P., Iribarren, M. J., de los Ríos, J. and Panadero, A. Changes in blood lactate, total body oxygen delivery and consumption during liver transplantation, (*ESA*) A.77
Carrera, J. *see* Monedero, P., (*ESA*) A.98
Carrera, J. A. *see* Catalá, J. C., (*ESA*) A.89
Cashman, J. N. *see* Lamond, C. T., (*ESA*) A.204
Castaigne, D. *see* Lequeau, F., (*ESA*) A.97
Castells, C. *see* Fernandez, D., (*ESA*) A.131
Catalá, J. *see* Monedero, P., (*ESA*) A.98
Catalá, J. C., Carrera, J. A., Iribarren, M. J., García Pedrajas, F. and Arroyo, J. L. Effects of diazepam additives on the mononuclear phagocytic system, (*ESA*) A.89
Catalá, J. C. *see* Hidalgo, F., (*ESA*) A.99
Catoire, P., Delaunay, L., Beydon, L., Guerrini, P. and Bonnet, F. Evaluation of systematic TEE in patients suspected of blunt chest trauma, (*ESA*) A.192
Catoire, P. *see* Fulgencio, J. P., (*ESA*) A.42; Liu, N., (*ESA*) A.25
Cattaneo, I., Kayser, V. and Guilbaud, G. Differential effects of specific delta and kappa opioid antagonists on the bidirectionnal effect of naloxone in arthritic rats, (*ESA*) A.114
Cavallier, S. *see* Riou, B., (*ESA*) A.102
Chabanne, J. P. *see* Descraques, C., (*ESA*) A.127
Chammas, E. *see* Bromberg, N., (*ESA*) A.28
Chataigneau, T. *see* Le Pelley, E., (*ESA*) A.48
Chauvin, M., Guirimand, F., Gauneau, P. and Lebrault, C. Effect of morphine on a nociceptive flexion reflex in patients with postoperative pain, (*ESA*) A.115
Chauvin, M. *see* Alfonsi, P., (*ESA*) A.74
Chazalet, J. J. *see* Jacob, L., (*ESA*) A.85
Cheema, S. P. S. *see* Entress, A. H., (*ESA*) A.158
Clacquin, C. *see* Samaha, T., (*ESA*) A.118
Clergue, F. *see* Mouquet, C., (*ESA*) A.83; Nyström, E., (*ESA*) A.65
Colardyn, F. *see* De Deyne, C., (*ESA*) A.16; (*ESA*) A.106
Collis, R. *see* Gan, T. J., (*ESA*) A.13
Comte, A. *see* Bazin, J. E., (*ESA*) A.136
Conseiller, C. T. *see* Vassilieff, N., (*ESA*) A.71
Constant, I. *see* Murat, I., (*ESA*) A.165
Coppo, F. *see* Py, C., (*ESA*) A.57
Coriat, P., Gomez, C., Daas, G., Perel, A. and Viars, P. The systolic pressure variation predicts response to volume loading in patients ventilated after aortic surgery, (*ESA*) A.38
Coriat, P. *see* Beaussier, M., (*ESA*) A.37; Gosgnach, M., (*ESA*) A.5; (*ESA*) A.6; Puybasset, L., (*ESA*) A.39
Cornet, A. *see* Thirion, A.-V., (*ESA*) A.172
Cortes, J. *see* Alvarez, J., (*ESA*) A.27
Cortiñas, J. *see* Alvarez, J., (*ESA*) A.27
Cosson, C. *see* Moulay, N., (*ESA*) A.108
Couarraze, G. *see* Benhamou, D., (*ESA*) A.120
Cozian, A. *see* Lepage, J. Y., (*ESA*) A.35
Cozzone, P. J. *see* Kozak Ribbens, G., (*ESA*) A.92
Crea, M. A., Sollazzi, L., Perilli, V., Marana, E. and Ranieri, R. Respiratory effects of laparoscopic cholecystectomy (preliminary data), (*ESA*) A.63
Croci, M. *see* Mulazzi, D., (*ESA*) A.54
Cunningham, A. *see* McCoy, D., (*ESA*) A.43

Daas, G. *see* Coriat, P., (*ESA*) A.38
Dandoy, M. *see* Lampl, E., (*ESA*) A.139
Debaene, B., Meistelman, C., Donati, F. and Lienhart, A. Monitoring the onset of neuromuscular blockade at the orbicularis oculi can predict good intubating conditions when using $2 \times ED_{95}$ of atracurium, (*ESA*) A.142
Debaene, B. *see* Plaud, B., (*ESA*) A.141
De Blasio, E. *see* Iannuzzi, E., (*ESA*) A.195
Debord, J. *see* Nathan, N., (*ESA*) A.151
Decoene, C. *see* Bromberg, N., (*ESA*) A.28
Decruyenaere, J. *see* De Deyne, C., (*ESA*) A.16; (*ESA*) A.106
De Deyne, C., Poelaert, J., Decruyenaere, J. and Colardyn, F. Technical aspects of jugular bulb oximetry, (*ESA*) A.16
De Deyne, C., Vandekerckhove, T., Decruyenaere, J., Poelaert, J. and Colardyn, F. Jugular bulb metabolic monitoring during hyperventilation in severe head trauma patients, (*ESA*) A.106
Degasperi, D., Vinelli, M., Festa, C. and Fiandri, M. T. Hypoxic events after general anaesthesia in the recovery room, (*ESA*) A.59
De Hert, S. G., Gillebert, T. C. and Brutsaert, D. L. Endocardial endothelium modulates *in vivo* left ventricular performance, (*ESA*) A.47
de Jong, J. R., Ros, H. H. and de Lange, J. J. Clinical evaluation of the calibration of noninvasive continuous blood pressure measurement devices by means of oscillometric blood pressure measurements, (*ESA*) A.15
de La Coussaye, J. E., Eledjam, J. J., Bruelle, P., Peray, P. and Sassine, A. Lemakalim reverses ventricular conduction impairment induced by a large dose of bupivacaine in anesthetized dogs, (*ESA*) A.121
de La Coussaye, J. E. *see* Lefrant, J. Y., (*ESA*) A.18
de Lange, J. J. *see* de Jong, J. R., (*ESA*) A.15; Wagemans, M. F. M., (*ESA*) A.213
de Lassale, M. E. *see* Rouby, J. J., (*ESA*) A.181
Delaunay, L. *see* Catoire, P., (*ESA*) A.192
Delayance, S., Mion, G., Mouren, S., Baron, J.-F., Diaby, M. and Viars, P. Effects of hypertonic saline on coronary blood flow and myocardial performance of a blood-perfused, isolated rabbit heart, (*ESA*) A.45
Delorme, M. *see* Murat, I., (*ESA*) A.166
De los Ríos, J., Iribarren, Mª J., Monedero, P., García-Pedrajas, F. and Arroyo, J. L. Modification of the renin–aldosterone axis during orthotopic liver transplantation, (*ESA*) A.75
de los Ríos, J. *see* Carrera, J., (*ESA*) A.77

Delva, E. *see* Camus, Y., (*ESA*) A.72; Lienhart, A., (*ESA*) A.93
Deriaz, H. *see* Duranteau, R., (*ESA*) A.148; Lienhart, A., (*ESA*) A.93
Dernovoi, B. S., Baurain, M. J., d'Hollander, A. A. and Bollen, P. C. Neostigmine antagonism of neuromuscular blockade induced by mivacurium, vecuronium and atracurium, (*ESA*) A.137
Dernovoi, B. S. *see* Baurain, M. J., (*ESA*) A.133; (*ESA*) A.134; (*ESA*) A.135
Desborough, J. P., Jones, P. M., Persaud, S. J. and Howell, S. L. Isoflurane inhibits Ca^{2+}-induced insulin secretion from electrically permeabilised islets of Langerhans, (*ESA*) A.91
Descoins, P. *see* Arné, J., (*ESA*) A.1
Descorps-Déclère, A. *see* Moulay, N., (*ESA*) A.108
Descraques, C., Mion, G., Auroy, Y., Lenoir, B., Pats, B., Rouvier, B. and Chabanne, J. P. Incidence of post dural puncture headache in young adults by the use of the Sprôtte needle: 300 patients, (*ESA*) A.127
De Sio, A. *see* Iannuzzi, E., (*ESA*) A.195
Desnault, H. *see* Lienhart, A., (*ESA*) A.93
De Zen, F. *see* Piccinni, P., (*ESA*) A.78
d'Hollander, A. *see* Bardoczky, G., (*ESA*) A.55; Engelman, E., (*ESA*) A.56
d'Hollander, A. A. *see* Baurain, M. J., (*ESA*) A.133; (*ESA*) A.134; (*ESA*) A.135; Dernovoi, B. S., (*ESA*) A.137
Diaby, M. *see* Delayance, S., (*ESA*) A.45; Fellahi, J. L., (*ESA*) A.44
Diamond, G. *see* Hohner, P., (*ESA*) A.41
Dittmann, M., Schäfer, H.-G., Renkl, F. and Greve, I. Nine years of clinical experience with 29 gauge spinal needles, (*ESA*) A.126
Do-Khac, T. *see* Bodin, L., (*ESA*) A.179
Donati, F. *see* Debaene, B., (*ESA*) A.142
Donnay, M. *see* Legros, F. J., (*ESA*) A.122
Drouet, L. O. *see* Samama, C. M., (*ESA*) A.100
Dubois, A. *see* Zaouk, G., (*ESA*) A.11
Dubois, M. C. *see* Murat, I., (*ESA*) A.166
Dubousset, A.-M. *see* Jamali, S., (*ESA*) A.160
Dubray, C. *see* Bazin, J. E., (*ESA*) A.136
Dupont, H., Nyarwaya, J.-B. and Samii, K. A comparison of midazolam and midazolam plus fentanyl for colonoscopy, (*ESA*) A.9
Dupuis, J. L. *see* Nathan, N., (*ESA*) A.151
Durak, P., Özgök, A., Esen, H., Erdemli, Ö and Ebil, S. The combined prophylactic administration of H1 and H2 receptor blockers in the prevention of protamine related haemodynamic effects and the relation between antihistaminics-leucocytes and pulmonary vascular resistance, (*ESA*) A.95
Durak, P., Özgök, A., Saydam, G., Türkmen, A., Erdemli, Ö. and Ebil, S. The relationship between cardiopulmonary bypass related immunologic effects and complement, thromboxane and leucocyte parameters, (*ESA*) A.96
Duranteau, R., Guesde, R., Riou, B., Deriaz, H. and Viars, P. Computer-controlled syringe pump improves safety of pharmacokinetic models, (*ESA*) A.148
Duranteau, R. *see* Riou, B., (*ESA*) A.80
Durbec, O. *see* Albanese, J., (*ESA*) A.107
Dwyer, R. *see* McCoy, D., (*ESA*) A.43
Dzoljic, M., Geller, E., Rupreht, J., Erdmann, W. and Dzoljic, M. R. Nitrous oxide induced neuronal depression: modification through benzodiazepine receptors, (*ESA*) A.112
Dzoljic, M. R. *see* Dzoljic, M., (*ESA*) A.112

Eberhard, A. *see* Py, C., (*ESA*) A.57
Ebil, S. *see* Durak, P., (*ESA*) A.95; (*ESA*) A.96
Ecoffey, C. *see* Auroy, Y., (*ESA*) A.76; Jamali, S., (*ESA*) A.160; Mahé, V., (*ESA*) A.109; Meistelman, C., (*ESA*) A.138; Moulay, N., (*ESA*) A.108; Nègre, I., (*ESA*) A.203; Orliaguet, G., (*ESA*) A.163; Reignier, J., (*ESA*) A.162; Samaha, T., (*ESA*) A.118
Edouard, A. *see* Mimoz, O., (*ESA*) A.180
Ehrenström Reiz, G. *see* Nath, S., (*ESA*) A.211
Ejlersen, E., Jensen, M. B. and Eliasen, K. Outcome for patients in intensive care with acute renal failure requiring dialysis, (*ESA*) A.7
Eldar, I. *see* Preisman, S., (*ESA*) A.124
Eledjam, J. J. *see* de La Coussaye, J. E., (*ESA*) A.121; Lefrant, J. Y., (*ESA*) A.18
Eleftheriadis, S., Kuppe, H., Klotz, K.-F. and Schmucker, P. Anesthesia for patients ≥ 90 years of age in emergency hip surgery, (*ESA*) A.3
Eleftheriadis, S. *see* Kuppe, H., (*ESA*) A.31
Elhaddoury, M. *see* Hamza, J., (*ESA*) A.171
Eliasen, K. *see* Ejlersen, E., (*ESA*) A.7
Engberg, G. *see* Rothen, H. U., (*ESA*) A.53
Engbers, F. *see* Boer, F., (*ESA*) A.147
Engelman, E., Bardoczky, G. and d'Hollander, A. Influence of posture on the respiratory mechanics during anesthesia, (*ESA*) A.56
Engelman, E. and Lipszyc, M. Effects of oral preoperative guanfacine on anesthetics requirements, (*ESA*) A.144
Engelman, E. *see* Bardoczky, G., (*ESA*) A.55
Entress, A. H. and Cheema, S. P. S. Use of thoracic epidural block for perioperative analgesia in children, (*ESA*) A.158
Erdemli, Ö *see* Durak, P., (*ESA*) A.95
Erdemli, Ö. *see* Durak, P., (*ESA*) A.96
Erdmann, W. *see* Dzoljic, M., (*ESA*) A.112
Ernst, E. *see* Morris, R. W., (*ESA*) A.2
Esen, H. *see* Durak, P., (*ESA*) A.95
Espadaler, J. M. *see* Fernandez, S., (*ESA*) A.119
Eurin, B. *see* Jacob, L., (*ESA*) A.85

Fargnoli, J. M. *see* Py, C., (*ESA*) A.57
Farhat, F. *see* Spencer, A., (*ESA*) A.207
Faris, P. P., Ritter, M., Abels, R. and Gordon, D. Effects of recombinant-human erythropoietin on postoperative transfusion requirements in subjects undergoing major orthopaedic surgery, (*ESA*) A.101
Faucon, G. *see* Freysz, M., (*ESA*) A.46
Feiss, P. *see* Nathan, N., (*ESA*) A.151
Fellahi, J. L., Ouardali, F., Mouren, S., Baron, J.-F., Diaby, M. and Viars, P. Functional recovery after 24 h preservation of rabbit hearts in University Wisconsin solution, (*ESA*) A.44
Felleiter, P., Breschinski, W. and Bock, K. H. Helicopter transportation of patients with symptomatic aortic aneurysms, (*ESA*) A.196
Fernandez, D., Castells, C., Rue, M., Bernaus, M. and Puig, M. M. Subarachnoid anaesthesia (SAA) and postoperative analgesia with bupivacaine (BV) plus fentanyl (FN) in geriatric patients, (*ESA*) A.131
Fernandez, S., Monells, J., Espadaler, J. M. and Puig, M. M. Effects of intrathecal meperidine (MP), fentanyl (FN) and lidocaine (LD) on somatosensory (SSEP) and cortical motor (CMEP) evoked potentials in humans, (*ESA*) A.119
Ferraro, F. *see* Iannuzzi, E., (*ESA*) A.195
Festa, C. *see* Degasperi, D., (*ESA*) A.59
Fiandri, M. T. *see* Degasperi, D., (*ESA*) A.59
Findley, I. L. *see* Bailey, C. R., (*ESA*) A.169
Fiset, P. *see* Meistelman, C., (*ESA*) A.138
Fleischer, F. *see* Rauch, H., (*ESA*) A.30
Fleron, M.-H. *see* Gosgnach, M., (*ESA*) A.5
Fogas, J. *see* Vereczkey, Z., (*ESA*) A.64
Foppoli, R, Lunghi, P., Bonara, Z., Mora, C. and Stacca, R. Fentanyl or buprenorphine side effects in spinal anaesthesia, (*ESA*) A.132
Forbes, D., Binning, A. and Scott, N. B. The effect of parenteral diclofenac and morphine on efficacy duration and height of blockade during continuous epidural bupivacaine 0.5%, (*ESA*) A.125
François, G. *see* Viviand, X., (*ESA*) A.150
Frankenberg, C. *see* Kulka, P. J., (*ESA*) A.143
Franklin, K. *see* Bålfors, E., (*ESA*) A.62
Freysz, M., Timour, Q., Bertrix, L., Loufoua, J. and Faucon, G. Pre- and intraoperative prevention by β-blockers, propranolol and esmolol, of ischaemia-induced ventricular fibrillation, (*ESA*) A.46
Friedman, A. *see* Hohner, P., (*ESA*) A.41
Frossard, J. *see* Meistelman, C., (*ESA*) A.138
Fulgencio, J. P., Rimaniol, J. M., Saada, M., Catoire, P. and Bonnet, F. Epidural clonidine and myocardial ischaemia after abdominal aortic surgery, (*ESA*) A.42
Fusciardi, J. *see* Arné, J., (*ESA*) A.1; Lacoste, L., (*ESA*) A.66; (*ESA*) A.67; Le Pelley, E., (*ESA*) A.48

Gallart, L. L. *see* Samsó, E., (*ESA*) A.205
Gan, T. J., Collis, R. and Hetreed, M. Double-blind comparison of ondansetron, droperidol and saline for prevention of nausea & vomiting after orthopaedic surgery, (*ESA*) A.13
Gannedahl, P. *see* Odeberg, S., (*ESA*) A.34
García Pedrajas, F. *see* Catalá, J. C., (*ESA*) A.89
García-Pedrajas, F. *see* De los Ríos, J., (*ESA*) A.75
Garrec, F. *see* Lepage, J. Y., (*ESA*) A.35
Gauneau, P. *see* Chauvin, M., (*ESA*) A.115
Gehring, H. *see* Kuppe, H., (*ESA*) A.31
Geiger, C., Kick, O., Böhrer, H., Motsch, J. and Martin, E. Comparison of ondansetron, metoclopramide and

droperidol for the prophylaxis of emetic symptoms after gynecological laparoscopic procedures, (*ESA*) A.14
Geißler, C. *see* Schregel, W., (*ESA*) A.105
Geller, E. *see* Dzoljic, M., (*ESA*) A.112
Georgiou, L., Vourlioti, A., Kremastinou, F., Stefanou, P. and Tsiotou, A. Influence of anaesthesia on post-operative hypoxaemia, (*ESA*) A.60
Gerling, W. *see* Kuppe, H., (*ESA*) A.31; Schäfer, R., (*ESA*) A.184
Gilbart, E. *see* Zaouk, G., (*ESA*) A.11
Gillart, T. *see* Bazin, J. E., (*ESA*) A.136
Gillebert, T. C. *see* De Hert, S. G., (*ESA*) A.47
Gillon, M.-C. *see* Auroy, Y., (*ESA*) A.76
Giron, G. P. *see* Armellin, G., (*ESA*) A.104; Marcassa, A., (*ESA*) A.168
Goarin, J. P., Le Bret, F., Jacquens, Y., Riou, B., Saada, M. and Viars, P. Diagnosis of aortic rupture by transesophageal echocardiography (TEE), (*ESA*) A.193
Goarin, J.-P. *see* Saada, M., (*ESA*) A.194; Vivien, B., (*ESA*) A.183
Gomez, C. *see* Coriat, P., (*ESA*) A.38
Gordon, D. *see* Faris, P. P., (*ESA*) A.101
Gosgnach, M., Bertrand, M., Pironkov, A., Coriat, P. and Viars, P. Does routine preoperative coronary angiography modify outcome after aortic surgery? (*ESA*) A.6
Gosgnach, M., Coriat, P., Fleron, M.-H., Bertrand, M. and Viars, P. Indications for coronary revascularisation in vascular surgical patients, (*ESA*) A.5
Gosgnach, M., Le Bret, F., Smail, N., Beaussier, M. and Viars, P. Tolerance of preoperative transesophageal echocardiography in patients scheduled for aortic surgery, (*ESA*) A.21
Gosgnach, M. *see* Beaussier, M., (*ESA*) A.37; Puybasset, L., (*ESA*) A.39
Gouin, F. *see* Martin, C., (*ESA*) A.20; (*ESA*) A.189; (*ESA*) A.190
Granry, J. C., Monrigal, C., Jacob, J. P. and Monrigal, J. P. Cerebral blood flow velocities (CBFV) during anaesthesia for gynaecological laparoscopic surgery, (*ESA*) A.32
Greaves, D. J. *see* Morris, R. W., (*ESA*) A.2
Green, T. *see* Bennett, S., (*ESA*) A.152
Greve, I. *see* Dittmann, M., (*ESA*) A.126
Grond, S. *see* Radbruch, L., (*ESA*) A.212
Guéneron, J. P. *see* Nègre, I., (*ESA*) A.203
Guerrero, M. *see* Riou, B., (*ESA*) A.103
Guerrini, P. *see* Catoire, P., (*ESA*) A.192
Guesde, R., Ourahma, S., Riou, B. and Viars, P. Effects of desmopressin (DDAVP) supplementation in brain dead organ donors (BDOD) on early recipient renal function, (*ESA*) A.79
Guesde, R. *see* Duranteau, R., (*ESA*) A.148; Riou, B., (*ESA*) A.80
Guidon-Attali, C. *see* Viviand, X., (*ESA*) A.150
Guilbaud, G. *see* Cattaneo, I., (*ESA*) A.114
Guirimand, F., Strimbu, M., Willer, J. C. and Le Bars, D. Involvement of μ, δ, and κ receptors in the inhibition by intrathecal morphine of a C-fibre evoked reflex in the rat, (*ESA*) A.116
Guirimand, F. *see* Chauvin, M., (*ESA*) A.115
Güzeldemir, M. E. *see* Bayhan, N., (*ESA*) A.123

Häggmark, S. *see* Hohner, P., (*ESA*) A.23; (*ESA*) A.26; (*ESA*) A.41; Reiz, S., (*ESA*) A.24; (*ESA*) A.52
Hak, A. *see* Boer, F., (*ESA*) A.147
Halliday, D. *see* Carli, F., (*ESA*) A.86
Hamilton-Davies, C. *see* Mythen, M., (*ESA*) A.29
Hamza, J., Narchi, P., Elhaddoury, M. and Benhamou, D. Adequate pain relief with epidural analgesia during labor: why are women still dissatisified? (*ESA*) A.171
Hamza, J. *see* Menigaux, C., (*ESA*) A.175
Hannemann, L. *see* Meier-Hellmann, A., (*ESA*) A.185; Spies, C., (*ESA*) A.186
Harf, A. *see* Beydon, L., (*ESA*) A.4
Haußmann, R. *see* Rauch, H., (*ESA*) A.30
Hawelski, T. *see* Pasch, T., (*ESA*) A.153
Hedenstierna, G. *see* Rothen, H. U., (*ESA*) A.53
Heil, T., Spies, C., Neumann, T. and Müller, C. Carbohydrate deficient transferrin: a new copredictor of alcoholism related postoperative complications? (*ESA*) A.88
Heil, T. *see* Spies, C., (*ESA*) A.110
Heiss-Dunlop, W. *see* Meier-Hellmann, A., (*ESA*) A.185
Hennart, D. and Mersch, Y. Analgesia by wound infiltration before or after surgery in inguinal herniorraphy, (*ESA*) A.202
Henry, M. *see* Thirion, A.-V., (*ESA*) A.172; Thormann, F., (*ESA*) A.173
Hetreed, M. *see* Gan, T. J., (*ESA*) A.13
Heytens, L. and Boosaert, L. Prolonged (> 1 week) sedation with midazolam in ICU patients: efficacy, safety and pharmacokinetics, (*ESA*) A.178
Hidalgo, F., Páramo, J. A., Catalá, J. C., Carrascosa, F. and Monedero, P. High dose aprotinin *versus* desmopressin acetate treatment in cardiac surgery, (*ESA*) A.99
Hohner, P., Backman, C., Diamond, G., Friedman, A., Häggmark, S., Johansson, G., Karp, K. and Reiz, S. Effects of nitrous oxide (N_2O) on systemic haemodynamics, regional left ventricular (LV) function and incidence of myocardial ischaemia (MI) in vascular surgical patients with coronary artery disease (CAD), (*ESA*) A.41
Hohner, P., Johansson, G., Häggmark, S., Mehta, V. and Reiz, S. Evaluation of haemodynamic indices of myocardial ischaemia in patients with coronary artery disease (CAD), (*ESA*) A.23
Hohner, P., Mehta, V., Saada, M., Häggmark, S., Jansson, E., Johansson, G. and Reiz, S. Sensitivity and specificity of mechanical and electrocardiographic myocardial ischaemia (MI) monitoring techniques, (*ESA*) A.26
Hohner, P. *see* Reiz, S., (*ESA*) A.24
Hongnat, J.-M. *see* Alfonsi, P., (*ESA*) A.74
Howell, S. L. *see* Desborough, J. P., (*ESA*) A.91

Iannuzzi, E., De Blasio, E., Ferraro, F., De Sio, A. and Schiraldi, F. The choice of ECM rate could improve the neuroprotection during CPR, (*ESA*) A.195
Ingrand, P. *see* Lacoste, L., (*ESA*) A.66
Innes, P., Allsop, E., Lockie, J., Kirton, C. and Booker, P. Comparison of dobutamine with enoximone following open heart surgery in small children, (*ESA*) A.167
Iribarren, Mª J. *see* De los Ríos, J., (*ESA*) A.75
Iribarren, M. J. *see* Carrera, J., (*ESA*) A.77
Iribarren, M. J. *see* Catalá, J. C., (*ESA*) A.89
Ivens, D. and Verborgh, C. Is correlation of arterial and end-tidal carbon dioxide pressure during inhalation anaesthesia better with laryngeal mask as compared to face mask? (*ESA*) A.17

Jacob, J. P. *see* Granry, J. C., (*ESA*) A.32
Jacob, L., Chazalet, J. J., Payen, D., Bedrossian, J., Teillac, P. and Eurin, B. Renal blood flow and function relationship in recent renal transplantation in man, (*ESA*) A.85
Jacobs, D. *see* Zaouk, G., (*ESA*) A.11
Jacquens, Y. *see* Goarin, J. P., (*ESA*) A.193; Riou, B., (*ESA*) A.80; Saada, M., (*ESA*) A.194
Jalkanen, L. *see* Meretoja, O. A., (*ESA*) A.140
Jamali, S., Monin, S., Begon, C., Dubousset, A.-M. and Ecoffey, C. Clonidine in paediatric caudal anaesthesia, (*ESA*) A.160
Jamali, S. *see* Nègre, I., (*ESA*) A.203
Jansson, E. *see* Hohner, P., (*ESA*) A.26; Nyström, E., (*ESA*) A.65
Jayr, C. *see* Spencer, A., (*ESA*) A.207
Jensen, M. B. *see* Ejlersen, E., (*ESA*) A.7
Johansson, G. *see* Hohner, P., (*ESA*) A.23; (*ESA*) A.26; (*ESA*) A.41; Österlund, B., (*ESA*) A.19; Reiz, S., (*ESA*) A.24; (*ESA*) A.52; Svanström, M., (*ESA*) A.177
Joly, L.-M. and Benhamou, D. Continuous monitoring of Sp_{O_2} during total intravenous anaesthesia with ketamine and spontaneous ventilation, (*ESA*) A.58
Jones, P. M. *see* Desborough, J. P., (*ESA*) A.91
Joos, S., Quintilla, R. and Servais, R. Sequential spinal peridural anaesthesia for gynaecological surgery under laparoscopy, (*ESA*) A.130
Joris, J. and Lamy, M. Neuroendocrine changes during pneumoperitoneum for laparoscopic cholecystectomy, (*ESA*) A.33

Kaddour, C. *see* Bodin, L., (*ESA*) A.191
Kalfon, P., Rouby, J. J. and Viars, P. Comparison of pressure support ventilation provided by two ICU ventilators, (*ESA*) A.182
Kalfon, P. *see* Beaussier, M., (*ESA*) A.37
Kanto, J. *see* Ali-Melkkilä, T., (*ESA*) A.145
Karalazos, L. *see* Skourtis, C., (*ESA*) A.36
Karayan, J. *see* Lacoste, L., (*ESA*) A.66; (*ESA*) A.67
Karling, M. A national database for intensive care medicine in Sweden, (*ESA*) A.8
Karling, M. *see* Östman, M., (*ESA*) A.22
Karp, K. *see* Hohner, P., (*ESA*) A.41; Östman, M., (*ESA*) A.22
Kaukinen, L. *see* Ojanen, R., (*ESA*) A.94

Kaukinen, S. *see* Ojanen, R., (*ESA*) A.94

Kayser, V. *see* Cattaneo, I., (*ESA*) A.114

Kendig, J. *see* Salonen, M., (*ESA*) A.113

Kermarec, N. *see* Liu, N., (*ESA*) A.128

Kermarrec, N. *see* Mahé, V., (*ESA*) A.109

Kick, O. *see* Geiger, C., (*ESA*) A.14

Kirton, C. *see* Innes, P., (*ESA*) A.167

Kirvelä, M., Yli-Hankala, A. and Lindgren, L. Total intravenous anaesthesia (TIVA) with propofol and alfentanil for renal transplantation, (*ESA*) A.81

Klotz, K.-F. *see* Eleftheriadis, S., (*ESA*) A.3; Kuppe, H., (*ESA*) A.31

Knapik, P., Richardson, J. B. and McLellan, I. Core–peripheral temperature difference in early *vs* later extubation after coronary artery surgery, (*ESA*) A.69; Early postperfusion assessment of gas exchange and postoperative extubation outcome following coronary artery surgery, (*ESA*) A.61

Kohn, W. *see* Perel, A., (*ESA*) A.117

Koscielniak-Nielsen, Z. J., Schierbeck, J., Stens Pedersen, H. L. and Perko, G. Flumazenil facilitates intraoperative arousal in scoliosis surgery, (*ESA*) A.157

Kozak Ribbens, G., Rodet, L., Borsarelli, J., Aubert, M. and Cozzone, P. J. Exercise and malignant hyperthermia: family investigations, (*ESA*) A.92

Kraemer, S. *see* Spies, C., (*ESA*) A.110

Krämer, J. *see* Striebel, H. W., (*ESA*) A.208

Kremastinou, F. *see* Georgiou, L., (*ESA*) A.60

Krivosic-Horber, R. *see* Bromberg, N., (*ESA*) A.28

Kulka, P. J., Tryba, M., Menzel, C., Leurs, F. and Frankenberg, C. Preoperative clonidine improves postoperative renal function in CABG patients, (*ESA*) A.143

Kulkarni, P. and Carli, F. Effectiveness of core warming on net transfer of body heat across the skin, (*ESA*) A.70

Kuppe, H., Klotz, K.-F., Eleftheriadis, S., Gehring, H. and Gerling, W. Accuracy of processed auditory evoked response in predicting movement during cardiac surgery, (*ESA*) A.31

Kuppe, H. *see* Eleftheriadis, S., (*ESA*) A.3

Lacarelle, B. *see* Viviand, X., (*ESA*) A.150

Lachatre, G. *see* Nathan, N., (*ESA*) A.151

Lacoste, L., Karayan, J., Lehuedé, M. S., Ingrand, P. and Fusciardi, J. Direct, indirect or flexible laryngoscopy after thyroidectomy? (*ESA*) A.66

Lacoste, L., Karayan, J., Thomas, D., Vallet, T. and Fusciardi, J. Day 0 or day 3 laryngoscopy after thyroidectomy? (*ESA*) A.67

Lafont, N. *see* Boogaerts, J., (*ESA*) A.200; Legros, F. J., (*ESA*) A.122

Lamas, G. *see* Bodin, L., (*ESA*) A.179

Lamond, C. T., Robinson, D. L., Boyd, J. T. and Cashman, J. N. Addition of droperidol to PCA morphine: what is the optimal dose? (*ESA*) A.204

Lampl, E. and Dandoy, M. Priming of atracurium with magnesium, (*ESA*) A.139

Lamy, M. *see* Joris, J., (*ESA*) A.33

Laurent, P. *see* Bodin, L., (*ESA*) A.179

Layfield, D. J. *see* Morris, R. W., (*ESA*) A.2

Le Bars, D. *see* Guirimand, F., (*ESA*) A.116

Lebrault, C. *see* Alfonsi, P., (*ESA*) A.74; Chauvin, M., (*ESA*) A.115

Le Bret, F. *see* Goarin, J. P., (*ESA*) A.193; Gosgnach, M., (*ESA*) A.21

Lefrant, J. Y., de La Coussaye, J. E., Aya, G., Saïssi, G. and Eledjam, J. J. Cardiac output (CO) measurement: comparison of esophageal Doppler (ED) *vs* thermodilution (TD), (*ESA*) A.18

Legros, F. J., Lafont, N., Donnay, M. and Boogaerts, J. Motor blockade and absence of local nerve toxicity induced by liposomal bupivacaine injected into the axillary brachial plexus of rabbits, (*ESA*) A.122

Legros, F. J. *see* Boogaerts, J., (*ESA*) A.200

Lehmann, K. A. *see* Radbruch, L., (*ESA*) A.212

Lehuedé, M. S. *see* Lacoste, L., (*ESA*) A.66

Lenoir, B. *see* Descraques, C., (*ESA*) A.127

Lenzlinger, P. M. *see* Alon, E., (*ESA*) A.12

Lepage, J. Y., Garrec, F., Malinovsky, J. M., Cozian, A. and Pinaud, M. Effects of plasma volume substitution on right ventricle volumes and function using Elohes® and Plasmion®, (*ESA*) A.35

Le Pelley, E., Chataigneau, T., Richer, J.-P., Tricoche, R. and Fusciardi, J. Does captopril modify the arterial response to vasopressor substances? (*ESA*) A.48

Lequeau, F., Bourgain, J. L., Castaigne, D. and Samama, M. Use of aprotinine during cytoreductive surgery of ovarian cancer, (*ESA*) A.97

Leurs, F. *see* Kulka, P. J., (*ESA*) A.143

Lherm, T. *see* Rouby, J. J., (*ESA*) A.181

Lienhart, A., Deriaz, H., Desnault, H., Masini, J. P. and Delva, E. Is Burkitt's lymphoma an etiology or a differential diagnosis of malignant hyperthermia? (*ESA*) A.93

Lienhart, A. *see* Camus, Y., (*ESA*) A.72; Debaene, B., (*ESA*) A.142; Vassilieff, N., (*ESA*) A.71

Lindgren, L. *see* Kirvelä, M., (*ESA*) A.81

Lipszyc, M. *see* Engelman, E., (*ESA*) A.144

Liu, N., Catoire, P., Rosso, J., Saada, M. and Bonnet, F. Evaluation in intensive care of the fraction area change obtained by automatic border detection, (*ESA*) A.25

Liu, N., Montefiore, A., Kermarec, N., Beydon, L. and Bonnet, F. Postdural puncture headaches are not related to the duration of spinal catheter placement, (*ESA*) A.128

Ljungqvist, O. *see* Odeberg, S., (*ESA*) A.34

Lockie, J. *see* Innes, P., (*ESA*) A.167

Lofaso, F. *see* Beydon, L., (*ESA*) A.4

Loufoua, J. *see* Freysz, M., (*ESA*) A.46

Luciani, J. *see* Mouquet, C., (*ESA*) A.82; (*ESA*) A.83

Lucke, F. *see* Savoia, G., (*ESA*) A.159

Luhmann, I. *see* Striebel, H. W., (*ESA*) A.208

Lundberg, J. *see* Raner, C., (*ESA*) A.49

Lunghi, P. *see* Foppoli, R, (*ESA*) A.132

Lyons, G. Best Quincke point needle for Caesarean section, (*ESA*) A.174

McCoy, D., O'Connor, M., Cunningham, A. and Dwyer, R. Influence of positive pressure ventilation on myocardial ischaemia after abdominal aortic aneurysm repair, (*ESA*) A.43

McLellan, I. *see* Knapik, P., (*ESA*) A.61; (*ESA*) A.69

Maghrebi, H. *see* Bodin, L., (*ESA*) A.191

Mahajan, R. P., Murty, G. E., Singh, P. and Aitkenhead, A. R. Laryngeal function as assessed by tussometry following topical anaesthesia, (*ESA*) A.68

Mahé, V., Kermarrec, N. and Ecoffey, C. External ventricular CSF drains infections, (*ESA*) A.109

Mahé, V. *see* Moulay, N., (*ESA*) A.108

Malinovsky, J. M. *see* Lepage, J. Y., (*ESA*) A.35

Malinowsky, J.-M. *see* Benhamou, D., (*ESA*) A.120

Marana, E. *see* Crea, M. A., (*ESA*) A.63

Marcassa, A., Sorbara, C., Stellin, G., Pittarello, D. and Giron, G. P. Extracorporeal membrane oxygenation for postoperative cardiac support in newborn infants: first clinical data, (*ESA*) A.168

Martin, C., Auffray, J.-P., Potié, F. and Gouin, F. Comparison of two therapeutic strategies of septic shock, (*ESA*) A.190

Martin, C., Papazian, L., Perrin, G., Saux, P. and Gouin, F. Preservation of humidity and heat of respiratory gases in patients with minute ventilation > 10 l/min, (*ESA*) A.20

Martin, C., Saux, P., Mege, J.-L., Perrin, G. and Gouin, F. Septic shock: effect of a goal-directed therapy on oxygen metabolism and serum cytokine levels, (*ESA*) A.189

Martin, C. *see* Albanese, J., (*ESA*) A.107; Viviand, X., (*ESA*) A.150

Martin, E. *see* Geiger, C., (*ESA*) A.14; Motsch, J., (*ESA*) A.155; Rauch, H., (*ESA*) A.30

Martínez, J. L. *see* Martínez Urionabarrenetxea, K., (*ESA*) A.187; Pérez Arancón, J. L., (*ESA*) A.188

Martínez Urionabarrenetxea, K., Pérez Arancón, J. L., Yoldi, J. I., Camarero, A. and Martínez, J. L. Molecular mediators and post-bacteraemic phase, (*ESA*) A.187

Martínez Urionabarrenetxea, K. *see* Pérez Arancón, J. L., (*ESA*) A.188

Martner, J. *see* Raner, C., (*ESA*) A.49; Sundeman, H., (*ESA*) A.50

Masini, J. P. *see* Lienhart, A., (*ESA*) A.93

Maze, M. *see* Salonen, M., (*ESA*) A.113

Mazoit, J. X. *see* Butscher, K., (*ESA*) A.201

Mazoyer, E. *see* Samama, C. M., (*ESA*) A.100

Mege, J.-L. *see* Martin, C., (*ESA*) A.189

Mehta, V. *see* Hohner, P., (*ESA*) A.23; (*ESA*) A.26

Meier-Hellmann, A., Hannemann, L., Weyandt, D., Heiss-Dunlop, W. and Reinhart, K. The effect of dobutamine and norepinephrine on global and splanchnic O_2 consumption, (*ESA*) A.185

Meistelman, C., Fiset, P., O'Kelly, B., Frossard, J., Plaud, B. and Ecoffey, C. The pharmacokinetics of rocuronium in pediatric patients: a pooled data analysis, (*ESA*) A.138

Meistelman, C. *see* Debaene, B., (*ESA*) A.142; Plaud, B., (*ESA*) A.141

Menigaux, C., Hamza, J., Bougnières, P. and Saint-Maurice, C. Neonatal glycemia: does the maternal i.v.

fluid regimen during labor make a difference? (*ESA*) A.175
Menzel, C. *see* Kulka, P. J., (*ESA*) A.143
Méray, J. *see* Vereczkey, Z., (*ESA*) A.64
Meretoja, O. A., Brandom, B. W., Taivainen, T. and Jalkanen, L. Supra-additivity between atracurium and vecuronium, (*ESA*) A.140
Mergaert, C., Rolly, G. and Versichelen, L. Target-controlled intravenous sedation with propofol, (*ESA*) A.149
Mersch, Y. *see* Hennart, D., (*ESA*) A.202
Messeter, K. *see* Åkeson, J., (*ESA*) A.111
Mestre, D. *see* Paut, O., (*ESA*) A.10
Michael, R. F. *see* Morris, R. W., (*ESA*) A.2
Mimoz, O., Edouard, A., Beydon, L., Bonnet, F. and Samii, K. Reassessment of bronchoalveolar lavage in the diagnosis of post traumatic pulmonary fat embolism, (*ESA*) A.180
Mion, G. *see* Delayance, S., (*ESA*) A.45; Descraques, C., (*ESA*) A.127
Monedero, P., Carrera, J., Catalá, J., Carrascosa, F. and Arroyo, J. L. Blood requirements reduction in orthotopic liver transplantation with aprotinin, (*ESA*) A.98
Monedero, P. *see* Carrera, J., (*ESA*) A.77; De los Ríos, J., (*ESA*) A.75; Hidalgo, F., (*ESA*) A.99
Monells, J. *see* Fernandez, S., (*ESA*) A.119
Monin, S. *see* Jamali, S., (*ESA*) A.160; Nègre, I., (*ESA*) A.203
Monrigal, C. *see* Granry, J. C., (*ESA*) A.32
Monrigal, J. P. *see* Granry, J. C., (*ESA*) A.32
Montasser, A. M. Propofol for tracheal intubation in paediatric outpatient anaesthesia, (*ESA*) A.161
Montefiore, A. *see* Liu, N., (*ESA*) A.128
Mora, C. *see* Foppoli, R, (*ESA*) A.132
Morris, R. W., Ernst, E., Greaves, D. J., Layfield, D. J. and Michael, R. F. An audit of the incidence and costs associated with post operative nausea and vomiting (PONV) following major gynaecological surgery in an inpatient population, (*ESA*) A.2
Motsch, J., Baller, S., Bach, A., Aderjan, R. and Martin, E. Midazolam premedication: a forensic approach to pharmacokinetics and amnesia, (*ESA*) A.155
Motsch, J. *see* Geiger, C., (*ESA*) A.14
Moulay, N., Mahé, V., Descorps-Déclère, A., Cosson, C. and Ecoffey, C. Cardiac function in aneurysmal subarachnoid haemorrhage, (*ESA*) A.108
Mouquet, C., Carayon, A., Clergue, F., Luciani, J., Bitker, M. and Viars, P. Volume loading and hormonal factors in the prevention of acute tubular necrosis in kidney transplantation, (*ESA*) A.83
Mouquet, C., Carayon, A., Ourahma, S., Bitker, M.-O. and Viars, P. Is the vasoconstrictive effect of cyclosporine mediated by endothelin in kidney transplantation? (*ESA*) A.84
Mouquet, C., Luciani, J., Bitker, M.-O. and Viars, P. Prevention of acute tubular necrosis by volume loading in kidney transplantation, (*ESA*) A.82
Mouren, S. *see* Delayance, S., (*ESA*) A.45; Fellahi, J. L., (*ESA*) A.44
Mourgeon, E. *see* Vivien, B., (*ESA*) A.183
Mulazzi, D., Calappi, E. and Croci, M. The respiratory compliance in normal and obese subjects during anaesthesia, (*ESA*) A.54
Müller, C. *see* Heil, T., (*ESA*) A.88
Muller, G. *see* Van Obbergh, L. J., (*ESA*) A.164
Murat, I., Bernière, J. and Constant, I. Evaluation of the efficacy of forced-air warmer (Bair Hugger) during spinal surgery in children, (*ESA*) A.165
Murat, I., Delorme, M., Piat, V. and Dubois, M. C. Evaluation of a forced-air warmer (Bair-Hugger) in maintaining body temperature in infants during cleft palate surgery, (*ESA*) A.166
Murga, G. *see* Samsó, E., (*ESA*) A.205
Murty, G. E. *see* Mahajan, R. P., (*ESA*) A.68
Mythen, M., Browne, D., Hamilton-Davies, C. and Webb, A. Gastric mucosal perfusion is better preserved during cardiac surgery when isoflurane rather than enflurane or propofol is used to maintain anaesthesia, (*ESA*) A.29

Narchi, P. *see* Aubrun, F., (*ESA*) A.198; Hamza, J., (*ESA*) A.171
Narcisse, F. *see* Nathan, N., (*ESA*) A.151
Nath, S. and Ehrenström Reiz, G. Treatment of cancer pain with morphine (MO)—A double blind study of extradural (ED) *versus* intramuscular (im) routes of administration, (*ESA*) A.211
Nathan, N., Debord, J., Narcisse, F., Dupuis, J. L., Lachatre, G. and Feiss, P. Pharmacokinetics of propofol and its conjugates after continuous infusion in normal and renal failure patients, (*ESA*) A.151
Nègre, I., Guéneron, J. P., Jamali, S., Monin, S. and Ecoffey, C. Preemptive analgesia with epidural morphine, (*ESA*) A.203
Nelson, V. *see* Bennett, S., (*ESA*) A.152
Neumann, T. *see* Heil, T., (*ESA*) A.88; Spies, C., (*ESA*) A.110
Nyarwaya, J.-B. *see* Dupont, H., (*ESA*) A.9
Nyström, E., Jansson, E., Wenngren, B.-I., Sharma, R., Clergue, F. and Reiz, S. Diaphragmatic function after bupivacaine cervical extradural analgesia for chronic pain therapy, (*ESA*) A.65
Nyström, E. *see* Reiz, S., (*ESA*) A.52

O'Connor, B. *see* Salonen, M., (*ESA*) A.113
O'Connor, M. *see* McCoy, D., (*ESA*) A.43
Odeberg, S., Ljungqvist, O., Gannedahl, P., Svenberg, T. and Sollevi, A. Influence of pneumoperitoneum and posture on hemodynamic and stress responses during anaesthesia for laparoscopic surgery, (*ESA*) A.34
Ojanen, R., Kaukinen, S., Seppälä, E., Kaukinen, L. and Vapaatalo, H. Inhibition of increase of blood thromboxane concentration by acetylsalicylic acid after release of tourniquet in lower extremity operations, (*ESA*) A.94
O'Kelly, B. *see* Meistelman, C., (*ESA*) A.138
Oris, B. *see* Puybasset, L., (*ESA*) A.39
Orliaguet, G., Plaud, B., Calmatte, S. and Ecoffey, C. Neuromuscular blockade following mivacurium in children during N_2O–halothane, (*ESA*) A.163
Österlund, B., Johansson, G. and Reiz, S. Cardiac output determined from pulmonary gas exchange, (*ESA*) A.19
Östman, M., Karling, M., Karp, K., Teien, D. and Reiz, S. Dipyridamole-TEE and 24 h Holter-ECG as preoperative screening tests for coronary artery disease in patients with abdominal aortic aneurysm, (*ESA*) A.22
Ouardali, F. *see* Fellahi, J. L., (*ESA*) A.44
Ourahma, S. *see* Guesde, R., (*ESA*) A.79; Mouquet, C., (*ESA*) A.84
Özgök, A. *see* Durak, P., (*ESA*) A.95; (*ESA*) A.96

Panadero, A. *see* Carrera, J., (*ESA*) A.77
Papazian, L. *see* Martin, C., (*ESA*) A.20
Páramo, J. A. *see* Hidalgo, F., (*ESA*) A.99
Pasch, T. and Hawelski, T. Propofol anaesthesia with spontaneous breathing for extracorporeal shock wave lithotripsy, (*ESA*) A.153
Pasch, T. *see* Alon, E., (*ESA*) A.12
Pats, B. *see* Descraques, C., (*ESA*) A.127
Paut, O., Vercher, J. L., Blin, O., Mestre, D. and Camboulives, J. Evaluation of saccadic eye movements as an objective test during recovery from anesthesia, (*ESA*) A.10
Payen, D. *see* Jacob, L., (*ESA*) A.85
Pendeville, P. E. *see* Van Boven, M. J., (*ESA*) A.87
Penzo, D. *see* Armellin, G., (*ESA*) A.104
Peray, P. *see* de La Coussaye, J. E., (*ESA*) A.121
Perdrix, J. P. *see* Py, C., (*ESA*) A.57
Perel, A., Shneider, A. and Kohn, W. Isoproterenol reverses the MAC decreasing effect of esmolol in rats, (*ESA*) A.117
Perel, A. *see* Coriat, P., (*ESA*) A.38; Preisman, S., (*ESA*) A.51; (*ESA*) A.124
Pérez Arancón, J. L., Martínez Urionabarrenetxea, K., Yoldi, J. I., Camarero, A. and Martínez, J. L. Molecular mediators and cardiac surgery, (*ESA*) A.188
Pérez Arancón, J. L. *see* Martínez Urionabarrenetxea, K., (*ESA*) A.187
Perilli, V. *see* Crea, M. A., (*ESA*) A.63
Perko, G. *see* Koscielniak-Nielsen, Z. J., (*ESA*) A.157
Perrin, G. *see* Martin, C., (*ESA*) A.20; (*ESA*) A.189
Persaud, S. J. *see* Desborough, J. P., (*ESA*) A.91
Pfeiffer, U. *see* Preisman, S., (*ESA*) A.51
Piat, V. *see* Murat, I., (*ESA*) A.166
Piccinni, P., Tripepi, A., Rossaro, L., De Zen, F. and Pierri, A. Oxygen consumption is dependent upon oxygen delivery in cirrhotics undergoing liver transplantation, (*ESA*) A.78
Pierri, A. *see* Piccinni, P., (*ESA*) A.78
Pietzsch, S. *see* Biro, P., (*ESA*) A.156
Pignaud, G. *see* Samama, C. M., (*ESA*) A.100
Pinaud, M. *see* Lepage, J. Y., (*ESA*) A.35
Pironkov, A. *see* Gosgnach, M., (*ESA*) A.6
Pitkänen, M. *see* Rosenberg, P. H., (*ESA*) A.129
Pittarello, D. *see* Armellin, G., (*ESA*) A.104; Marcassa, A., (*ESA*) A.168
Plaud, B., Proost, J. H., Wierda, J. M. K. H., Debaene, B., Barré, J. and Meistelman, C. Concentration–effect

relationship at the vocal cords and the adductor pollicis following rocuronium administration, (*ESA*) A.141
Plaud, B. *see* Meistelman, C., (*ESA*) A.138; Orliaguet, G., (*ESA*) A.163
Poelaert, J. *see* De Deyne, C., (*ESA*) A.16; (*ESA*) A.106
Poete, P. *see* Rouby, J. J., (*ESA*) A.181
Pol, A. *see* Bromberg, N., (*ESA*) A.28
Pommerening, J. *see* Striebel, W. H., (*ESA*) A.209
Portilla, M. *see* Beaussier, M., (*ESA*) A.37
Potié, F. *see* Martin, C., (*ESA*) A.190
Preisman, S., Eldar, I. and Perel, A. The effects of epidural and spinal anesthesia on the changes in the plethysmographic signal in the lower and upper limbs, (*ESA*) A.124
Preisman, S., Shneider, A., Pfeiffer, U. and Perel, A. A comparison between various hemodynamic parameters reflecting preload during traded hemorrhage in ventilated dogs, (*ESA*) A.51
Proost, J. H. *see* Plaud, B., (*ESA*) A.141
Puig, M. M. *see* Fernandez, D., (*ESA*) A.131; Fernandez, S., (*ESA*) A.119; Samsó, E., (*ESA*) A.205
Puybasset, L., Oris, B., Coriat, P., Gosgnach, M. and Viars, P. Influence of chronic angiotensin converting enzyme inhibition on systolic pressure variation during anesthetic induction, (*ESA*) A.39
Py, C., Perdrix, J. P., Baconnier, P., Eberhard, A., Fargnoli, J. M., Coppo, F. and Banssillon, V. Continuous monitoring of the ventilatory mechanics during anaesthesia & intensive care, (*ESA*) A.57

Quinquis, V. *see* Benhamou, D., (*ESA*) A.120
Quintilla, R. *see* Joos, S., (*ESA*) A.130

Radbruch, L., Grond, S., Zech, D. and Lehmann, K. A. High dose oral morphine in cancer pain management, (*ESA*) A.212
Ramachandra, V. *see* Bennet, J., (*ESA*) A.73
Ramos, M. *see* Riou, B., (*ESA*) A.103
Raner, C., Biber, B., Lundberg, J., Martner, J. and Winsö, O. Does exogenous dopamine reverse cardiovascular depression induced by isoflurane during thoracic epidural blockade? (*ESA*) A.49
Raner, C. *see* Sundeman, H., (*ESA*) A.50
Ranieri, R. *see* Crea, M. A., (*ESA*) A.63
Rauch, H., Fleischer, F., Haußmann, R., Böttiger, B. and Martin, E. Propofol/fentanyl-anesthesia in patients with highly depressed cardiac function, (*ESA*) A.30
Rauss, A. *see* Beydon, L., (*ESA*) A.4
Ravussin, P. *see* Samaha, T., (*ESA*) A.118
Rawal, N. Organization of acute pain services—a low-cost model, (*ESA*) A.199
Read, M. *see* Carli, F., (*ESA*) A.86
Reignier, J., Ben Ameur, M. and Ecoffey, C. Ventilation with halothane is less affected in children with laryngeal mask airway than with endotracheal tube, (*ESA*) A.162
Reinhart, K. *see* Meier-Hellmann, A., (*ESA*) A.185; Spies, C., (*ESA*) A.110; (*ESA*) A.186
Reiz, S., Johansson, G., Hohner, P. and Häggmark, S. The use of the CUSUM plot for determination of myocardial ischaemia threshold during atrial pacing in patients with coronary artery disease, (*ESA*) A.24
Reiz, S., Nyström, E., Tugrul, M., Häggmark, S. and Johansson, G. Influence of cervicothoracic epidural anaesthesia (C-TEA) on left ventricular (LV) contractility—an experimental study in pigs with autonomous blockade, (*ESA*) A.52
Reiz, S. *see* Hohner, P., (*ESA*) A.26; (*ESA*) A.41; Nyström, E., (*ESA*) A.65; Österlund, B., (*ESA*) A.19; Östman, M., (*ESA*) A.22
Renkl, F. *see* Dittmann, M., (*ESA*) A.126
Richardson, J. B. *see* Knapik, P., (*ESA*) A.61; (*ESA*) A.69
Richer, J.-P. *see* Le Pelley, E., (*ESA*) A.48
Rieger, A. *see* Striebel, W. H., (*ESA*) A.209; (*ESA*) A.210
Riez, S. *see* Hohner, P., (*ESA*) A.23
Rimaniol, J. M. *see* Fulgencio, J. P., (*ESA*) A.42
Riou, B., Cavallier, S., Roy-Camille, R. and Viars, P. Preoperative autotransfusion in emergency surgery for spine trauma, (*ESA*) A.102
Riou, B., Guerrero, M., Arock, M., Ramos, M. and Viars, P. Effects of postoperative auto-transfusion in spine surgery, (*ESA*) A.103
Riou, B., Guesde, R., Jacquens, Y., Duranteau, R. and Viars, P. Fiberoptic bronchoscopy in brain dead organ donors, (*ESA*) A.80
Riou, B. *see* Duranteau, R., (*ESA*) A.148; Goarin, J. P., (*ESA*) A.193; Guesde, R., (*ESA*) A.79; Saada, M., (*ESA*) A.194
Ritter, M. *see* Faris, P. P., (*ESA*) A.101
Robinson, D. L. *see* Lamond, C. T., (*ESA*) A.204
Rodet, L. *see* Kozak Ribbens, G., (*ESA*) A.92
Rohierse-Hohler, I. *see* Striebel, H. W., (*ESA*) A.208
Rolly, G. *see* Mergaert, C., (*ESA*) A.149; Van Bastelaere, M., (*ESA*) A.146
Ros, H. H. *see* de Jong, J. R., (*ESA*) A.15
Rosenberg, P. H., Taivainen, T., Pitkänen, M. and Tuominen, M. Epidural blood patch for treatment of postdural puncture headache, (*ESA*) A.129
Rosencher, N. *see* Vassilieff, N., (*ESA*) A.71
Rossaro, L. *see* Piccinni, P., (*ESA*) A.78
Rosso, J. *see* Liu, N., (*ESA*) A.25
Rothen, H. U., Sporre, B., Engberg, G., Wegenius, G. and Hedenstierna, G. Recruitment of atelectasis during general anaesthesia: a CT-study, (*ESA*) A.53
Rouby, J. J., Lherm, T., de Lassale, M. E., Poete, P., Bodin, L. and Viars, P. Histology aspects of pulmonary barotrauma in critically ill patients with acute respiratory failure, (*ESA*) A.181
Rouby, J. J. *see* Bodin, L., (*ESA*) A.179; (*ESA*) A.191; Kalfon, P., (*ESA*) A.182
Rouby, J.-J. *see* Saada, M., (*ESA*) A.194; Vivien, B., (*ESA*) A.183
Rouvier, B. *see* Descraques, C., (*ESA*) A.127
Roy-Camille, R. *see* Riou, B., (*ESA*) A.102
Rue, M. *see* Fernandez, D., (*ESA*) A.131
Ruggier, R. *see* Bailey, C. R., (*ESA*) A.169
Rupreht, J. *see* Dzoljic, M., (*ESA*) A.112

Saada, M., Riou, B., Goarin, J.-P., Rouby, J.-J., Jacquens, Y. and Viars, P. Systemic gas embolism in pulmonary contusion diagnosed by transesophageal echocardiography, (*ESA*) A.194
Saada, M. *see* Fulgencio, J. P., (*ESA*) A.42; Goarin, J. P., (*ESA*) A.193; Hohner, P., (*ESA*) A.26; Liu, N., (*ESA*) A.25; Vivien, B., (*ESA*) A.183
Saint-Maurice, C. *see* Menigaux, C., (*ESA*) A.175
Saïssi, G. *see* Lefrant, J. Y., (*ESA*) A.18
Salonen, M., Kendig, J., O'Connor, B. and Maze, M. Dexmedetomidine does not exercise its anesthetic action through GABA, (*ESA*) A.113
Samaha, T., Ravussin, P., Clacquin, C. and Ecoffey, C. Effect of esmolol *versus* lidocaine on intracranial pressure and haemodynamic responses to laryngoscopy and intubation, (*ESA*) A.118
Samama, C. M., Mazoyer, E., Bruneval, P., Bonnin, P., Bonneau, M., Pignaud, G., Viars, P., Caen, J. P. and Drouet, L. O. Aprotinin does not decrease surgical bleeding and could promote arterial thrombosis in the pig: A prospective randomized, blind, study, (*ESA*) A.100
Samama, M. *see* Lequeau, F., (*ESA*) A.97
Samii, K. *see* Butscher, K., (*ESA*) A.201; Dupont, H., (*ESA*) A.9; Mimoz, O., (*ESA*) A.180
Samsó, E., Murga, G., Valles, J., Gallart, L. L. and Puig, M. M. Effects of epidural clonidine on anaesthetic requirements and postoperative analgesia, (*ESA*) A.205
Sansone, A. *see* Santangelo, E., (*ESA*) A.206; Savoia, G., (*ESA*) A.159
Santangelo, E., Amantea, B., Sansone, A., Savoia, G. and Sparacia, B. Safety of PCA in elderly, (*ESA*) A.206
Sassine, A. *see* de La Coussaye, J. E., (*ESA*) A.121
Saux, P. *see* Martin, C., (*ESA*) A.20; (*ESA*) A.189
Savoia, G., Lucke, F., Sparacia, B. and Sansone, A. Blended anaesthesia in pediatric major surgery: top-up *vs* epidural continuous infusion, (*ESA*) A.159
Savoia, G. *see* Santangelo, E., (*ESA*) A.206
Saydam, G. *see* Durak, P., (*ESA*) A.96
Schäfer, H.-G. *see* Dittmann, M., (*ESA*) A.126
Schäfer, R., Gerling, W., Utschakowski, A. and Wagner, K. Influence of norepinephrine therapy on the oxygen supply and lactate extraction rate of the liver in the septic pig, (*ESA*) A.184
Schäfermeyer, H. *see* Schregel, W., (*ESA*) A.105
Schierbeck, J. *see* Koscielniak-Nielsen, Z. J., (*ESA*) A.157
Schiraldi, F. *see* Iannuzzi, E., (*ESA*) A.195
Schmartz, D. M. *see* Baurain, M. J., (*ESA*) A.133; (*ESA*) A.135
Schmucker, P. *see* Eleftheriadis, S., (*ESA*) A.3
Schoeffler, P. *see* Bazin, J. E., (*ESA*) A.136
Schregel, W., Geißler, C., Bredenkötter, U. and Schäfermeyer, H. Transcranial Doppler sonography: effect of propofol and thiopental in patients with brain tumors and brain injuries, (*ESA*) A.105
Scott, N. B. *see* Forbes, D., (*ESA*) A.125
Seebacher, J. *see* Thirion, A.-V., (*ESA*) A.172; Thormann, F., (*ESA*) A.173
Seppälä, E. *see* Ojanen, R., (*ESA*) A.94
Sermeus, L. *see* Wiebalck, A., (*ESA*) A.90; (*ESA*) A.154

Servais, R. *see* Joos, S., (*ESA*) A.130
Sessler, D. I. *see* Vassilieff, N., (*ESA*) A.71
Setzis, D. *see* Skourtis, C., (*ESA*) A.36
Sharma, R. *see* Nyström, E., (*ESA*) A.65
Shneider, A. *see* Perel, A., (*ESA*) A.117; Preisman, S., (*ESA*) A.51
Singelyn, F. J. *see* Van Boven, M. J., (*ESA*) A.87
Singh, P. *see* Mahajan, R. P., (*ESA*) A.68
Skourtis, C., Karalazos, L. and Setzis, D. Alternating right to left ventricular ejection; the case of occult cardiac tamponade, (*ESA*) A.36
Smail, N. *see* Gosgnach, M., (*ESA*) A.21
Smilov, I. and Borissov, B. Epidural clonidine analgesia after major gynaecological surgery, (*ESA*) A.176
Soini, H. *see* Ali-Melkkilä, T., (*ESA*) A.145
Soler, J. P. *see* Thormann, F., (*ESA*) A.173
Sollazzi, L. *see* Crea, M. A., (*ESA*) A.63
Sollevi, A. *see* Odeberg, S., (*ESA*) A.34
Sorbara, C. *see* Armellin, G., (*ESA*) A.104; Marcassa, A., (*ESA*) A.168
Sparacia, B. *see* Santangelo, E., (*ESA*) A.206; Savoia, G., (*ESA*) A.159
Spencer, A., Farhat, F., Bourgain, J.-L. and Jayr, C. Postoperative hypoxaemia: comparison of epidural and patient controlled analgesia, (*ESA*) A.207
Spies, C., Kraemer, S., Heil, T., Neumann, T. and Reinhart, K. EEG-monitoring during defibrillator-implantation: effects of repetitive cerebral ischemia on electric brain activity, (*ESA*) A.110
Spies, C., Witt, I., Walensky, C., Hannemann, L. and Reinhart, K. Influence of N-acetylcysteine on O_2 consumption and gastric intramucosal pH in septic patients, (*ESA*) A.186
Spies, C. *see* Heil, T., (*ESA*) A.88
Spoelder, E. M. *see* Wagemans, M. F. M., (*ESA*) A.213
Sporre, B. *see* Rothen, H. U., (*ESA*) A.53
Stacca, R. *see* Foppoli, R, (*ESA*) A.132
Stefanou, P. *see* Georgiou, L., (*ESA*) A.60
Stellin, G. *see* Marcassa, A., (*ESA*) A.168
Stens Pedersen, H. L. *see* Koscielniak-Nielsen, Z. J., (*ESA*) A.157
Striebel, H. W., Krämer, J., Luhmann, I., Rohierse-Hohler, I. and Triltsch, A. Pharmacokinetics of intranasal fentanyl, (*ESA*) A.208
Striebel, W. H., Pommerening, J., Rieger, A. and Brummer, G. Intranasal fentanyl for postoperative pain management in an unselected population, (*ESA*) A.209
Striebel, W. H., Wessel, A., Rieger, A. and Boerger, N. Intranasal fentanyl for breakthrough cancer pain or incident pain, (*ESA*) A.210
Strimbu, M. *see* Guirimand, F., (*ESA*) A.116
Sundeman, H., Biber, B., Winsö, S., Martner, J. and Raner, C. Local *versus* neurogenic vasodilator effects of desflurane and isoflurane in the small intestine, (*ESA*) A.50
Svanström, M., Johansson, G. and Bålfors, E. Mechanisms of ECG changes during caesarean section (CS)—a hypothesis, (*ESA*) A.177
Svenberg, T. *see* Odeberg, S., (*ESA*) A.34

Taivainen, T. *see* Meretoja, O. A., (*ESA*) A.140; Rosenberg, P. H., (*ESA*) A.129
Teien, D. *see* Östman, M., (*ESA*) A.22
Teillac, P. *see* Jacob, L., (*ESA*) A.85
Thirion, A.-V., Henry, M., Cornet, A., Seebacher, J. and Viars, P. Spinal anesthesia for C section: addition of phenylephrine to ephedrine for prevention of maternal hypotension, (*ESA*) A.172
Thomas, D. *see* Lacoste, L., (*ESA*) A.67
Thormann, F., Henry, M., Soler, J. P., Seebacher, J. and Viars, P. Headache—new needles and spinal anaesthesia for C. section, (*ESA*) A.173
Timour, Q. *see* Freysz, M., (*ESA*) A.46
Tricoche, R. *see* Le Pelley, E., (*ESA*) A.48
Triltsch, A. *see* Striebel, H. W., (*ESA*) A.208
Tripepi, A. *see* Piccinni, P., (*ESA*) A.78
Tryba, M. *see* Kulka, P. J., (*ESA*) A.143
Tsiotou, A. *see* Georgiou, L., (*ESA*) A.60
Tugrul, M. *see* Reiz, S., (*ESA*) A.52
Tuominen, M. *see* Rosenberg, P. H., (*ESA*) A.129
Türkan, H. *see* Bayhan, N., (*ESA*) A.123
Türkmen, A. *see* Durak, P., (*ESA*) A.96

Utschakowski, A. *see* Schäfer, R., (*ESA*) A.184

Valles, J. *see* Samsó, E., (*ESA*) A.205
Vallet, T. *see* Lacoste, L., (*ESA*) A.67
Vanacker, B. *see* Wiebalck, A., (*ESA*) A.90; (*ESA*) A.154
Van Aken, H. *see* Baudot, J., (*ESA*) A.170; Blockmans, D., (*ESA*) A.40; Wiebalck, A., (*ESA*) A.90; (*ESA*) A.154
Van Bastelaere, M., Rolly, G. and Van Peer, A. Pharmacokinetic behaviour of transdermal fentanyl, (*ESA*) A.146
Van Boven, M. J., Pendeville, P. E. and Singelyn, F. J. Glycine and its metabolites during and after intrauterine YAG laser surgery, (*ESA*) A.87
Vandekerckhove, T. *see* De Deyne, C., (*ESA*) A.106
Van Hemelrijck, J. *see* Blockmans, D., (*ESA*) A.40
Van Obbergh, L. J., Zeippen, B., Muller, G. and Veyckemans, F. Relationship between arterial $P\text{co}_2$ (Pa_{CO_2}) and end tidal CO_2 (ETco_2) recorded through a laryngeal mask (LMA) in children breathing spontaneously, (*ESA*) A.164
Van Peer, A. *see* Van Bastelaere, M., (*ESA*) A.146
Vapaatalo, H. *see* Ojanen, R., (*ESA*) A.94
Vassilieff, N., Rosencher, N., Sessler, D. I., Conseiller, C. T. and Lienhart, A. Effect of premedication with nifedipine on intraoperative hypothermia, (*ESA*) A.71
Verborgh, C. *see* Ivens, D., (*ESA*) A.17
Vercher, J. L. *see* Paut, O., (*ESA*) A.10
Vereczkey, Z., Babik, B., Fogas, J., Méray, J. and Baltás, B. Abdominal wall retraction may decrease anaesthesiological risks of laparoscopic cholecystectomy, (*ESA*) A.64
Versichelen, L. *see* Mergaert, C., (*ESA*) A.149
Vertommen, J. D. *see* Baudot, J., (*ESA*) A.170
Veyckemans, F. *see* Van Obbergh, L. J., (*ESA*) A.164
Viars, P. *see* Beaussier, M., (*ESA*) A.37; Bodin, L., (*ESA*) A.179; (*ESA*) A.191; Coriat, P., (*ESA*) A.38; Delayance, S., (*ESA*) A.45; Duranteau, R., (*ESA*) A.148; Fellahi, J. L., (*ESA*) A.44; Goarin, J. P., (*ESA*) A.193; Gosgnach, M., (*ESA*) A.5; (*ESA*) A.6; (*ESA*) A.21; Guesde, R., (*ESA*) A.79; Kalfon, P., (*ESA*) A.182; Mouquet, C., (*ESA*) A.82; (*ESA*) A.83; (*ESA*) A.84; Puybasset, L., (*ESA*) A.39; Riou, B., (*ESA*) A.80; (*ESA*) A.102; (*ESA*) A.103; Rouby, J. J., (*ESA*) A.181; Saada, M., (*ESA*) A.194; Samama, C. M., (*ESA*) A.100; Thirion, A.-V., (*ESA*) A.172; Thormann, F., (*ESA*) A.173; Vivien, B., (*ESA*) A.183
Vinelli, M. *see* Degasperi, D., (*ESA*) A.59
Virkkilä, M. *see* Ali-Melkkilä, T., (*ESA*) A.145
Viviand, X., Guidon-Attali, C., Lacarelle, B., Martin, C. and François, G. Determination of a pharmacokinetic model for propofol induction of anaesthesia, (*ESA*) A.150
Viviand, X. *see* Albanese, J., (*ESA*) A.107
Vivien, B., Mourgeon, E., Saada, M., Goarin, J.-P., Rouby, J.-J. and Viars, P. Evaluation of cardiac function in ICU: right heart catheterization *vs* transesophageal echocardiography. Preliminary results, (*ESA*) A.183
Vourlioti, A. *see* Georgiou, L., (*ESA*) A.60

Wagemans, M. F. M., Zuurmond, W. W. A., Spoelder, E. M. and de Lange, J. J. Intrathecal pain relief in terminally ill cancer patients at home, (*ESA*) A.213
Wagner, K. *see* Schäfer, R., (*ESA*) A.184
Walensky, C. *see* Spies, C., (*ESA*) A.186
Webb, A. *see* Mythen, M., (*ESA*) A.29
Wegenius, G. *see* Rothen, H. U., (*ESA*) A.53
Weidmann, G. *see* Biro, P., (*ESA*) A.156
Wenker, O. The part of rescue helicopters in large accidents and disasters, (*ESA*) A.197
Wenngren, B.-I. *see* Nyström, E., (*ESA*) A.65
Wessel, A. *see* Striebel, W. H., (*ESA*) A.210
Weyandt, D. *see* Meier-Hellmann, A., (*ESA*) A.185
Wiebalck, A., Vanacker, B., Van Aken, H., Sermeus, L., Bouillon, R. and Amery, A. Adrenocortical function: a clinical comparison of Etomidat-Lipuro® and Hypnomidate®, (*ESA*) A.90; Quality of Induction: a clinical comparison of Etomidat-Lipuro® and Hypnomidate®, (*ESA*) A.154
Wierda, J. M. K. H. *see* Plaud, B., (*ESA*) A.141
Willer, J. C. *see* Guirimand, F., (*ESA*) A.116
Winsö, O. *see* Raner, C., (*ESA*) A.49
Winsö, S. *see* Sundeman, H., (*ESA*) A.50
Witt, I. *see* Spies, C., (*ESA*) A.186

Yli-Hankala, A. *see* Kirvelä, M., (*ESA*) A.81
Yoldi, J. I. *see* Martínez Urionabarrenetxea, K., (*ESA*) A.187; Pérez Arancón, J. L., (*ESA*) A.188

Zaouk, G., Gilbart, E., Dubois, A., Jacobs, D. and Balatoni, E. Alizapride does reduce pain on injection of propofol: comparison with lidocaine, (*ESA*) A.11
Zech, D. *see* Radbruch, L., (*ESA*) A.212
Zeippen, B. *see* Van Obbergh, L. J., (*ESA*) A.164
Zouaoui, Z. *see* Bodin, L., (*ESA*) A.179
Zuurmond, W. W. A. *see* Wagemans, M. F. M., (*ESA*) A.213

SUBJECT INDEX

Acid–base equilibrium, Changes in blood lactate, total body oxygen delivery and consumption during liver transplantation, Carrera, J., *et al.*, (*ESA*) A.77

Acid–base equilibrium, pH, Measurement of sigmoid intramural pH during orthotopic liver transplantation, Auroy, Y., *et al.*, (*ESA*) A.76

Adductor pollicis, Can repetition of high frequencies stimuli alter the value of 50 and 100 Hz tetanic fade during vecuronium induced neuromuscular blockade? Baurain, M. J., *et al.*, (*ESA*) A.135

——, Concentration–effect relationship at the vocal cords and the adductor pollicis following rocuronium administration, Plaud, B., *et al.*, (*ESA*) A.141

——, Monitoring the onset of neuromuscular blockade at the orbicularis oculi can predict good intubating conditions when using $2 \times ED_{95}$ of atracurium, Debaene, B., *et al.*, (*ESA*) A.142

Age factors, An investigation into the effect of passive and active cutaneous warming devices on intraoperative body temperature in elderly patients, Bennet, J., *et al.*, (*ESA*) A.73

——, Anesthesia for patients ⩾ 90 years of age in emergency hip surgery, Eleftheriadis, S., *et al.*, (*ESA*) A.3

——, Effectiveness of core warming on net transfer of body heat across the skin, Kulkarni, P., *et al.*, (*ESA*) A.70

——, Incidence of post dural puncture headache in young adults by the use of the Sprôtte needle: 300 patients, Descraques, C., *et al.*, (*ESA*) A.127

——, Ketamine does not prevent hypotension caused by induction of anaesthesia with propofol in elderly patients, Blockmans, D., *et al.*, (*ESA*) A.40

——, Safety of PCA in elderly, Santangelo, E., *et al.*, (*ESA*) A.206

——, The pharmacokinetics of rocuronium in pediatric patients: a pooled data analysis, Meistelman, C., *et al.*, (*ESA*) A.138

Airway, anatomy, A new clinical score to predict difficult intubation, Arné, J., *et al.*, (*ESA*) A.1

Airway, infections, A new clinical score to predict difficult intubation, Arné, J., *et al.*, (*ESA*) A.1

Airway, patency, Continuous spirometry: an aid in the intraoperative respiratory monitoring—case reports, Bardoczky, G., *et al.*, (*ESA*) A.55

Alcohol, withdrawal, Carbohydrate deficient transferrin: a new copredictor of alcoholism related postoperative complications? Heil, T., *et al.*, (*ESA*) A.88

Anaesthesia, audit, Adequate pain relief with epidural analgesia during labor: why are women still dissatisified? Hamza, J., *et al.*, (*ESA*) A.171

——, An audit of the incidence and costs associated with post operative nausea and vomiting (PONV) following major gynaecological surgery in an inpatient population, Morris, R. W., *et al.*, (*ESA*) A.2

Anaesthesia, day-case, Propofol for tracheal intubation in paediatric outpatient anaesthesia, Montasser, A. M., (*ESA*) A.161

Anaesthesia, general, Hypoxic events after general anaesthesia in the recovery room, Degasperi, D., *et al.*, (*ESA*) A.59

——, Recruitment of atelectasis during general anaesthesia: a CT-study, Rothen, H. U., *et al.*, (*ESA*) A.53

Anaesthesia, geriatric, Anesthesia for patients ⩾ 90 years of age in emergency hip surgery, Eleftheriadis, S., *et al.*, (*ESA*) A.3

——, Fentanyl or buprenorphine side effects in spinal anaesthesia, Foppoli, R, *et al.*, (*ESA*) A.132

——, Ketamine does not prevent hypotension caused by induction of anaesthesia with propofol in elderly patients, Blockmans, D., *et al.*, (*ESA*) A.40

——, Subarachnoid anaesthesia (SAA) and postoperative analgesia with bupivacaine (BV) plus fentanyl (FN) in geriatric patients, Fernandez, D., *et al.*, (*ESA*) A.131

Anaesthesia, neurosurgical, Effect of esmolol *versus* lidocaine on intracranial pressure and haemodynamic responses to laryngoscopy and intubation, Samaha, T., *et al.*, (*ESA*) A.118

Anaesthesia, obstetric, Best Quincke point needle for Caesarean section, Lyons, G., (*ESA*) A.174

——, Headache—new needles and spinal anaesthesia for C. section, Thormann, F., *et al.*, (*ESA*) A.173

——, Mechanisms of ECG changes during caesarean section (CS)—a hypothesis, Svanström, M., *et al.*, (*ESA*) A.177

——, Spinal anesthesia for C section: addition of phenylephrine to ephedrine for prevention of maternal hypotension, Thirion, A.-V., *et al.*, (*ESA*) A.172

Anaesthesia, paediatric, Blended anaesthesia in pediatric major surgery: top-up *vs* epidural continuous infusion, Savoia, G., *et al.*, (*ESA*) A.159

——, Clonidine in paediatric caudal anaesthesia, Jamali, S., *et al.*, (*ESA*) A.160

——, Continuous monitoring of Sp_{O_2} during total intravenous anaesthesia with ketamine and spontaneous ventilation, Joly, L.-M., *et al.*, (*ESA*) A.58

——, Propofol for tracheal intubation in paediatric outpatient anaesthesia, Montasser, A. M., (*ESA*) A.161

——, Relationship between arterial $P\text{CO}_2$ (Pa_{CO_2}) and end tidal CO_2 (ETco_2) recorded through a laryngeal mask (LMA) in children breathing spontaneously, Van Obbergh, L. J., *et al.*, (*ESA*) A.164

——, Ventilation with halothane is less affected in children with laryngeal mask airway than with endotracheal tube, Reignier, J., *et al.*, (*ESA*) A.162

Anaesthetic–analgesic regimens, Addition of droperidol to PCA morphine: what is the optimal dose? Lamond, C. T., *et al.*, (*ESA*) A.204

——, Blended anaesthesia in pediatric major surgery: top-up *vs* epidural continuous infusion, Savoia, G., *et al.*, (*ESA*) A.159

——, Diamorphine/bupivacaine mixture *vs* plain bupivacaine: a comparison of epidural infusions in labour, Bailey, C. R., *et al.*, (*ESA*) A.169

——, Fentanyl or buprenorphine side effects in spinal anaesthesia, Foppoli, R, *et al.*, (*ESA*) A.132

——, Postoperative hypoxaemia: comparison of epidural and patient controlled analgesia, Spencer, A., *et al.*, (*ESA*) A.207

——, Propofol anaesthesia with spontaneous breathing for extracorporeal shock wave lithotripsy, Pasch, T., *et al.*, (*ESA*) A.153

——, Subarachnoid anaesthesia (SAA) and postoperative analgesia with bupivacaine (BV) plus fentanyl (FN) in geriatric patients, Fernandez, D., *et al.*, (*ESA*) A.131

Anaesthetic techniques, bronchoscopy, Fiberoptic bronchoscopy in brain dead organ donors, Riou, B., *et al.*, (*ESA*) A.80

Anaesthetic techniques, extradural, Blended anaesthesia in pediatric major surgery: top-up *vs* epidural continuous infusion, Savoia, G., *et al.*, (*ESA*) A.159

——, Does exogenous dopamine reverse cardiovascular depression induced by isoflurane during thoracic epidural blockade? Raner, C., *et al.*, (*ESA*) A.49

——, Effects of epidural clonidine on anaesthetic requirements and postoperative analgesia, Samsó, E., *et al.*, (*ESA*) A.205

——, Epidural blood patch for treatment of postdural puncture headache, Rosenberg, P. H., *et al.*, (*ESA*) A.129

——, Influence of cervicothoracic epidural anaesthesia (C-TEA) on left ventricular (LV) contractility—an experimental study in pigs with autonomous blockade, Reiz, S., *et al.*, (*ESA*) A.52

——, Sequential spinal peridural anaesthesia for gynaecological surgery under laparoscopy, Joos, S., *et al.*, (*ESA*) A.130

——, The effect of parenteral diclofenac and morphine on efficacy duration and height of blockade during continuous epidural bupivacaine 0.5%, Forbes, D., *et al.*, (*ESA*) A.125

——, The effects of epidural and spinal anesthesia on the changes in the plethysmographic signal in the lower and upper limbs, Preisman, S., *et al.*, (*ESA*) A.124

Anaesthetic techniques, fibreoptic, Direct, indirect or flexible laryngoscopy after thyroidectomy? Lacoste, L., *et al.*, (*ESA*) A.66

Anaesthetic techniques, hypotensive, Does nicardipine potentiate the neuromuscular block of atracurium? Bazin, J. E., *et al.*, (*ESA*) A.136

Anaesthetic techniques, hypothermia, Core–peripheral temperature difference in early *vs* later extubation after coronary artery surgery, Knapik, P., *et al.*, (*ESA*) A.69

Anaesthetic techniques, i.m., Slow-release effect of pH-adjusted bupivacaine: pharmacokinetic demonstration, Benhamou, D., *et al.*, (*ESA*) A.120

Anaesthetic techniques, induction, Determination of a pharmacokinetic model for propofol induction of anaesthesia, Viviand, X., *et al.*, (*ESA*) A.150

——, Quality of Induction: a clinical comparison of Etomidat-Lipuro® and Hypnomidate®, Wiebalck, A., *et al.*, (*ESA*) A.154

Anaesthetic techniques, inhalation, Influence of anaesthesia on post-operative hypoxaemia, Georgiou, L., *et al.*, (*ESA*) A.60

——, Is correlation of arterial and end-tidal carbon dioxide pressure during inhalation anaesthesia better with laryngeal mask as compared to face mask? Ivens, D., *et al.*, (*ESA*) A.17

——, Ventilation with halothane is less affected in children with laryngeal mask airway than with endotracheal tube, Reignier, J., *et al.*, (*ESA*) A.162

Anaesthetic techniques, insufflation, Abdominal wall retraction may decrease anaesthesiological risks of laparoscopic cholecystectomy, Vereczkey, Z., *et al.*, (*ESA*) A.64

——, Influence of pneumoperitoneum and posture on hemodynamic and stress responses during anaesthesia for laparoscopic surgery, Odeberg, S., *et al.*, (*ESA*) A.34

——, Neuroendocrine changes during pneumoperitoneum for laparoscopic cholecystectomy, Joris, J., *et al.*, (*ESA*) A.33

——, Respiratory effects of laparoscopic cholecystectomy (preliminary data), Crea, M. A., *et al.*, (*ESA*) A.63

Anaesthetic techniques, i.v., Continuous monitoring of Sp_{O_2} during total intravenous anaesthesia with ketamine and spontaneous ventilation, Joly, L.-M., *et al.*, (*ESA*) A.58

——, Influence of anaesthesia on post-operative hypoxaemia, Georgiou, L., *et al.*, (*ESA*) A.60

——, Total intravenous anaesthesia (TIVA) with propofol and alfentanil for renal transplantation, Kirvelä, M., *et al.*, (*ESA*) A.81

Anaesthetic techniques, i.v. infusion, Computer-controlled syringe pump improves safety of pharmacokinetic models, Duranteau, R., *et al.*, (*ESA*) A.148

——, Determination of a pharmacokinetic model for propofol induction of anaesthesia, Viviand, X., *et al.*, (*ESA*) A.150

——, Pharmacokinetics of propofol and its conjugates after continuous infusion in normal and renal failure patients, Nathan, N., *et al.*, (*ESA*) A.151

——, Prolonged (> 1 week) sedation with midazolam in ICU patients: efficacy, safety and pharmacokinetics, Heytens, L., *et al.*, (*ESA*) A.178

——, Propofol anaesthesia with spontaneous breathing for extracorporeal shock wave lithotripsy, Pasch, T., *et al.*, (*ESA*) A.153

Anaesthetic techniques, laryngoscopy, Day 0 or day 3 laryngoscopy after thyroidectomy? Lacoste, L., *et al.*, (*ESA*) A.67

——, Direct, indirect or flexible laryngoscopy after thyroidectomy? Lacoste, L., *et al.*, (*ESA*) A.66

Anaesthetic techniques, regional, brachial plexus, Motor blockade and absence of local nerve toxicity induced by liposomal bupivacaine injected into the axillary brachial plexus of rabbits, Legros, F. J., *et al.*, (*ESA*) A.122

Anaesthetic techniques, regional, caudal, Clonidine in paediatric caudal anaesthesia, Jamali, S., *et al.*, (*ESA*) A.160

Anaesthetic techniques, subarachnoid, Best Quincke point needle for Caesarean section, Lyons, G., (*ESA*) A.174

——, Effects of intrathecal meperidine (MP), fentanyl (FN) and lidocaine (LD) on somatosensory (SSEP) and cortical motor (CMEP) evoked potentials in humans, Fernandez, S., *et al.*, (*ESA*) A.119

——, Fentanyl or buprenorphine side effects in spinal anaesthesia, Foppoli, R, *et al.*, (*ESA*) A.132

——, Headache—new needles and spinal anaesthesia for C. section, Thormann, F., *et al.*, (*ESA*) A.173

——, Incidence of post dural puncture headache in young adults by the use of the Sprôtte needle: 300 patients, Descraques, C., *et al.*, (*ESA*) A.127

——, Nine years of clinical experience with 29 gauge spinal needles, Dittmann, M., *et al.*, (*ESA*) A.126

——, Postdural puncture headaches are not related to the duration of spinal catheter placement, Liu, N., *et al.*, (*ESA*) A.128

——, Sequential spinal peridural anaesthesia for gynaecological surgery under laparoscopy, Joos, S., *et al.*, (*ESA*) A.130

——, Spinal anesthesia for C section: addition of phenylephrine to ephedrine for prevention of maternal hypotension, Thirion, A.-V., *et al.*, (*ESA*) A.172

——, Subarachnoid anaesthesia (SAA) and postoperative analgesia with bupivacaine (BV) plus fentanyl (FN) in geriatric patients, Fernandez, D., *et al.*, (*ESA*) A.131

——, The effects of epidural and spinal anesthesia on the changes in the plethysmographic signal in the lower and upper limbs, Preisman, S., *et al.*, (*ESA*) A.124

Anaesthetic techniques, topical, Laryngeal function as assessed by tussometry following topical anaesthesia, Mahajan, R. P., *et al.*, (*ESA*) A.68

Anaesthetics gases, nitrous oxide, Effects of nitrous oxide (N_2O) on systemic haemodynamics, regional left ventricular (LV) function and incidence of myocardial ischaemia (MI) in vascular surgical patients with coronary artery disease (CAD), Hohner, P., *et al.*, (*ESA*) A.41

——, Influence of anaesthesia on post-operative hypoxaemia, Georgiou, L., *et al.*, (*ESA*) A.60

——, Neuromuscular blockade following mivacurium in children during N_2O–halothane, Orliaguet, G., *et al.*, (*ESA*) A.163

——, Nitrous oxide induced neuronal depression: modification through benzodiazepine receptors, Dzoljic, M., *et al.*, (*ESA*) A.112

Anaesthetics i.v., droperidol, Addition of droperidol to PCA morphine: what is the optimal dose? Lamond, C. T., *et al.*, (*ESA*) A.204

——, Comparison of ondansetron, metoclopramide and droperidol for the prophylaxis of emetic symptoms after gynecological laparoscopic procedures, Geiger, C., *et al.*, (*ESA*) A.14

——, Double-blind comparison of ondansetron, droperidol and saline for prevention of nausea & vomiting after orthopaedic surgery, Gan, T. J., *et al.*, (*ESA*) A.13

——, Ondansetron 4 mg *vs* droperidol 1.25 mg in the prophylaxis of postoperative nausea and vomiting after alfentanil-supplemented inhalation anaesthesia, Alon, E., *et al.*, (*ESA*) A.12

Anaesthetics i.v., etomidate, Adrenocortical function: a clinical comparison of Etomidat-Lipuro® and Hypnomidate®, Wiebalck, A., *et al.*, (*ESA*) A.90

——, Quality of Induction: a clinical comparison of Etomidat-Lipuro® and Hypnomidate®, Wiebalck, A., *et al.*, (*ESA*) A.154

Anaesthetics i.v., ketamine, Continuous monitoring of Sp_{O_2} during total intravenous anaesthesia with ketamine and spontaneous ventilation, Joly, L.-M., *et al.*, (*ESA*) A.58

——, Ketamine does not prevent hypotension caused by induction of anaesthesia with propofol in elderly patients, Blockmans, D., *et al.*, (*ESA*) A.40

——, Midazolam prevents ketamine-induced stimulation of cerebral metabolism, Åkeson, J., *et al.*, (*ESA*) A.111

Anaesthetics i.v., propofol, Alizapride does reduce pain on injection of propofol: comparison with lidocaine, Zaouk, G., *et al.*, (*ESA*) A.11

——, Determination of a pharmacokinetic model for propofol induction of anaesthesia, Viviand, X., *et al.*, (*ESA*) A.150

——, Gastric mucosal perfusion is better preserved during cardiac surgery when isoflurane rather than enflurane or propofol is used to maintain anaesthesia, Mythen, M., *et al.*, (*ESA*) A.29

——, Influence of anaesthesia on post-operative hypoxaemia, Georgiou, L., *et al.*, (*ESA*) A.60

——, Ketamine does not prevent hypotension caused by induction of anaesthesia with propofol in elderly patients, Blockmans, D., *et al.*, (*ESA*) A.40

——, Pharmacokinetics of propofol and its conjugates after continuous infusion in normal and renal failure patients, Nathan, N., *et al.*, (*ESA*) A.151

——, Propofol (2,6 diisopropylphenol) as an antioxidant *in-vitro*: a dose response study, Bennett, S., *et al.*, (*ESA*) A.152

——, Propofol anaesthesia with spontaneous breathing for extracorporeal shock wave lithotripsy, Pasch, T., *et al.*, (*ESA*) A.153

——, Propofol for tracheal intubation in paediatric outpatient anaesthesia, Montasser, A. M., (*ESA*) A.161

——, Propofol/fentanyl-anesthesia in patients with highly depressed cardiac function, Rauch, H., *et al.*, (*ESA*) A.30

——, Target-controlled intravenous sedation with propofol, Mergaert, C., *et al.*, (*ESA*) A.149

——, Total intravenous anaesthesia (TIVA) with propofol and alfentanil for renal transplantation, Kirvelä, M., *et al.*, (*ESA*) A.81

——, Transcranial Doppler sonography: effect of propofol and

thiopental in patients with brain tumors and brain injuries, Schregel, W., *et al.*, (*ESA*) A.105
Anaesthetics i.v., thiopentone, Transcranial Doppler sonography: effect of propofol and thiopental in patients with brain tumors and brain injuries, Schregel, W., *et al.*, (*ESA*) A.105
Anaesthetics local, bupivacaine, Analgesia by wound infiltration before or after surgery in inguinal hernioraphy, Hennart, D., *et al.*, (*ESA*) A.202
——, Blended anaesthesia in pediatric major surgery: top-up *vs* epidural continuous infusion, Savoia, G., *et al.*, (*ESA*) A.159
——, Diamorphine/bupivacaine mixture *vs* plain bupivacaine: a comparison of epidural infusions in labour, Bailey, C. R., *et al.*, (*ESA*) A.169
——, Diaphragmatic function after bupivacaine cervical extradural analgesia for chronic pain therapy, Nyström, E., *et al.*, (*ESA*) A.65
——, Epidural administration of liposomal bupivacaine for the management of postsurgical pain, Boogaerts, J., *et al.*, (*ESA*) A.200
——, Fentanyl or buprenorphine side effects in spinal anaesthesia, Foppoli, R, *et al.*, (*ESA*) A.132
——, Lemakalim reverses ventricular conduction impairment induced by a large dose of bupivacaine in anesthetized dogs, de La Coussaye, J. E., *et al.*, (*ESA*) A.121
——, Motor blockade and absence of local nerve toxicity induced by liposomal bupivacaine injected into the axillary brachial plexus of rabbits, Legros, F. J., *et al.*, (*ESA*) A.122
——, Patient controlled epidural analgesia *vs* intermittent injections during labor using 0.125% bupivacaine and sufentanil, Baudot, J., *et al.*, (*ESA*) A.170
——, Postoperative hypoxaemia: comparison of epidural and patient controlled analgesia, Spencer, A., *et al.*, (*ESA*) A.207
——, Slow-release effect of pH-adjusted bupivacaine: pharmacokinetic demonstration, Benhamou, D., *et al.*, (*ESA*) A.120
——, Subarachnoid anaesthesia (SAA) and postoperative analgesia with bupivacaine (BV) plus fentanyl (FN) in geriatric patients, Fernandez, D., *et al.*, (*ESA*) A.131
——, The effect of parenteral diclofenac and morphine on efficacy duration and height of blockade during continuous epidural bupivacaine 0.5%, Forbes, D., *et al.*, (*ESA*) A.125
——, The effects of bupivacaine, mepivacaine and prilocaine on platelet aggregation, Bayhan, N., *et al.*, (*ESA*) A.123
——, Use of thoracic epidural block for perioperative analgesia in children, Entress, A. H., *et al.*, (*ESA*) A.158
Anaesthetics local, lignocaine, Alizapride does reduce pain on injection of propofol: comparison with lidocaine, Zaouk, G., *et al.*, (*ESA*) A.11
——, Effect of esmolol *versus* lidocaine on intracranial pressure and haemodynamic responses to laryngoscopy and intubation, Samaha, T., *et al.*, (*ESA*) A.118
——, Effects of intrathecal meperidine (MP), fentanyl (FN) and lidocaine (LD) on somatosensory (SSEP) and cortical motor (CMEP) evoked potentials in humans, Fernandez, S., *et al.*, (*ESA*) A.119
——, Fentanyl, as pethidine, inhibits post anaesthesia shivering, Alfonsi, P., *et al.*, (*ESA*) A.74
——, Laryngeal function as assessed by tussometry following topical anaesthesia, Mahajan, R. P., *et al.*, (*ESA*) A.68
Anaesthetics local, mepivacaine, The effects of bupivacaine, mepivacaine and prilocaine on platelet aggregation, Bayhan, N., *et al.*, (*ESA*) A.123
Anaesthetics local, prilocaine, The effects of bupivacaine, mepivacaine and prilocaine on platelet aggregation, Bayhan, N., *et al.*, (*ESA*) A.123
Anaesthetics volatile, desflurane, Local *versus* neurogenic vasodilator effects of desflurane and isoflurane in the small intestine, Sundeman, H., *et al.*, (*ESA*) A.50
Anaesthetics volatile, enflurane, Effects of oral preoperative guanfacine on anesthetics requirements, Engelman, E., *et al.*, (*ESA*) A.144
——, Gastric mucosal perfusion is better preserved during cardiac surgery when isoflurane rather than enflurane or propofol is used to maintain anaesthesia, Mythen, M., *et al.*, (*ESA*) A.29
Anaesthetics volatile, halothane, Isoproterenol reverses the MAC decreasing effect of esmolol in rats, Perel, A., *et al.*, (*ESA*) A.117
——, Neuromuscular blockade following mivacurium in children during N_2O–halothane, Orliaguet, G., *et al.*, (*ESA*) A.163
——, Ventilation with halothane is less affected in children with laryngeal mask airway than with endotracheal tube, Reignier, J., *et al.*, (*ESA*) A.162
Anaesthetics volatile, isoflurane, Does exogenous dopamine reverse cardiovascular depression induced by isoflurane during thoracic epidural blockade? Raner, C., *et al.*, (*ESA*) A.49
——, Effects of oral preoperative guanfacine on anesthetics requirements, Engelman, E., *et al.*, (*ESA*) A.144
——, Gastric mucosal perfusion is better preserved during cardiac surgery when isoflurane rather than enflurane or propofol is used to maintain anaesthesia, Mythen, M., *et al.*, (*ESA*) A.29
——, Influence of anaesthesia on post-operative hypoxaemia, Georgiou, L., *et al.*, (*ESA*) A.60
——, Isoflurane inhibits Ca^{2+}-induced insulin secretion from electrically permeabilised islets of Langerhans, Desborough, J. P., *et al.*, (*ESA*) A.91
——, Local *versus* neurogenic vasodilator effects of desflurane and isoflurane in the small intestine, Sundeman, H., *et al.*, (*ESA*) A.50
Analgesia, geriatric, Subarachnoid anaesthesia (SAA) and postoperative analgesia with bupivacaine (BV) plus fentanyl (FN) in geriatric patients, Fernandez, D., *et al.*, (*ESA*) A.131
Analgesia, obstetric, Adequate pain relief with epidural analgesia during labor: why are women still dissatisified? Hamza, J., *et al.*, (*ESA*) A.171
——, Diamorphine/bupivacaine mixture *vs* plain bupivacaine: a comparison of epidural infusions in labour, Bailey, C. R., *et al.*, (*ESA*) A.169
——, Patient controlled epidural analgesia *vs* intermittent injections during labor using 0.125% bupivacaine and sufentanil, Baudot, J., *et al.*, (*ESA*) A.170
Analgesia, paediatric, Clonidine in paediatric caudal anaesthesia, Jamali, S., *et al.*, (*ESA*) A.160
——, Use of thoracic epidural block for perioperative analgesia in children, Entress, A. H., *et al.*, (*ESA*) A.158
Analgesia, patient-controlled, Addition of droperidol to PCA morphine: what is the optimal dose? Lamond, C. T., *et al.*, (*ESA*) A.204
——, Patient controlled epidural analgesia *vs* intermittent injections during labor using 0.125% bupivacaine and sufentanil, Baudot, J., *et al.*, (*ESA*) A.170
——, Postoperative hypoxaemia: comparison of epidural and patient controlled analgesia, Spencer, A., *et al.*, (*ESA*) A.207
——, Safety of PCA in elderly, Santangelo, E., *et al.*, (*ESA*) A.206
Analgesia, postoperative, Addition of droperidol to PCA morphine: what is the optimal dose? Lamond, C. T., *et al.*, (*ESA*) A.204
——, Clonidine in paediatric caudal anaesthesia, Jamali, S., *et al.*, (*ESA*) A.160
——, Effect of morphine on a nociceptive flexion reflex in patients with postoperative pain, Chauvin, M., *et al.*, (*ESA*) A.115
——, Effects of epidural clonidine on anaesthetic requirements and postoperative analgesia, Samsó, E., *et al.*, (*ESA*) A.205
——, Epidural administration of liposomal bupivacaine for the management of postsurgical pain, Boogaerts, J., *et al.*, (*ESA*) A.200
——, Evaluation of pain and analgesia in a postanesthesia care unit, Aubrun, F., *et al.*, (*ESA*) A.198
——, Intranasal fentanyl for postoperative pain management in an unselected population, Striebel, W. H., *et al.*, (*ESA*) A.209
——, Organization of acute pain services—a low-cost model, Rawal, N., (*ESA*) A.199
——, Postoperative analgesia: a two dosage regimens trial for i.m. morphine after early i.v. titration, Butscher, K., *et al.*, (*ESA*) A.201
——, Subarachnoid anaesthesia (SAA) and postoperative analgesia with bupivacaine (BV) plus fentanyl (FN) in geriatric patients, Fernandez, D., *et al.*, (*ESA*) A.131
——, The effect of parenteral diclofenac and morphine on efficacy duration and height of blockade during continuous epidural bupivacaine 0.5%, Forbes, D., *et al.*, (*ESA*) A.125
Analgesia, pre-emptive, Analgesia by wound infiltration before or after surgery in inguinal hernioraphy, Hennart, D., *et al.*, (*ESA*) A.202
——, Preemptive analgesia with epidural morphine, Nègre, I., *et al.*, (*ESA*) A.203
Analgesic techniques, extradural, Adequate pain relief with epidural analgesia during labor: why are women still dissatisified? Hamza, J., *et al.*, (*ESA*) A.171
——, Diamorphine/bupivacaine mixture *vs* plain bupivacaine: a comparison of epidural infusions in labour, Bailey, C. R., *et al.*, (*ESA*) A.169
——, Diaphragmatic function after bupivacaine cervical

extradural analgesia for chronic pain therapy, Nyström, E., *et al.*, (*ESA*) A.65
——, Epidural administration of liposomal bupivacaine for the management of postsurgical pain, Boogaerts, J., *et al.*, (*ESA*) A.200
——, Epidural clonidine analgesia after major gynaecological surgery, Smilov, I., *et al.*, (*ESA*) A.176
——, Epidural clonidine and myocardial ischaemia after abdominal aortic surgery, Fulgencio, J. P., *et al.*, (*ESA*) A.42
——, Patient controlled epidural analgesia *vs* intermittent injections during labor using 0.125% bupivacaine and sufentanil, Baudot, J., *et al.*, (*ESA*) A.170
——, Postoperative hypoxaemia: comparison of epidural and patient controlled analgesia, Spencer, A., *et al.*, (*ESA*) A.207
——, Preemptive analgesia with epidural morphine, Nègre, I., *et al.*, (*ESA*) A.203
——, Use of thoracic epidural block for perioperative analgesia in children, Entress, A. H., *et al.*, (*ESA*) A.158
Analgesic techniques, i.m., Pharmacokinetics and effects of i.m. alfentanil as premedication for outpatient cataract surgery, Ali-Melkkilä, T., *et al.*, (*ESA*) A.145
Analgesic techniques, infiltration, Analgesia by wound infiltration before or after surgery in inguinal hernioraphy, Hennart, D., *et al.*, (*ESA*) A.202
Analgesic techniques, infusion, Intrathecal pain relief in terminally ill cancer patients at home, Wagemans, M. F. M., *et al.*, (*ESA*) A.213
Analgesic techniques, nasal, Intranasal fentanyl for breakthrough cancer pain or incident pain, Striebel, W. H., *et al.*, (*ESA*) A.210
——, Intranasal fentanyl for postoperative pain management in an unselected population, Striebel, W. H., *et al.*, (*ESA*) A.209
——, Pharmacokinetics of intranasal fentanyl, Striebel, H. W., *et al.*, (*ESA*) A.208
Analgesic techniques, patient-controlled, Intrathecal pain relief in terminally ill cancer patients at home, Wagemans, M. F. M., *et al.*, (*ESA*) A.213
Analgesic techniques, subarachnoid, Intrathecal pain relief in terminally ill cancer patients at home, Wagemans, M. F. M., *et al.*, (*ESA*) A.213
——, Involvement of μ, δ, and κ receptors in the inhibition by intrathecal morphine of a C-fibre evoked reflex in the rat, Guirimand, F., *et al.*, (*ESA*) A.116
Analgesics non-opioid, diclofenac, The effect of parenteral diclofenac and morphine on efficacy duration and height of blockade during continuous epidural bupivacaine 0.5%, Forbes, D., *et al.*, (*ESA*) A.125
Analgesics non-opioid, ketorolac, Safety of PCA in elderly, Santangelo, E., *et al.*, (*ESA*) A.206
Analgesics opioid, alfentanil, Effects of oral preoperative guanfacine on anesthetics requirements, Engelman, E., *et al.*, (*ESA*) A.144
——, Ondansetron 4 mg *vs* droperidol 1.25 mg in the prophylaxis of postoperative nausea and vomiting after alfentanil-supplemented inhalation anaesthesia, Alon, E., *et al.*, (*ESA*) A.12
——, Pharmacokinetic behaviour of transdermal fentanyl, Van Bastelaere, M., *et al.*, (*ESA*) A.146
——, Pharmacokinetics and effects of i.m. alfentanil as premedication for outpatient cataract surgery, Ali-Melkkilä, T., *et al.*, (*ESA*) A.145
——, Quality of Induction: a clinical comparison of Etomidat-Lipuro® and Hypnomidate®, Wiebalck, A., *et al.*, (*ESA*) A.154
——, Total intravenous anaesthesia (TIVA) with propofol and alfentanil for renal transplantation, Kirvelä, M., *et al.*, (*ESA*) A.81
Analgesics opioid, buprenorphine, Blended anaesthesia in pediatric major surgery: top-up *vs* epidural continuous infusion, Savoia, G., *et al.*, (*ESA*) A.159
——, Fentanyl or buprenorphine side effects in spinal anaesthesia, Foppoli, R, *et al.*, (*ESA*) A.132
——, Safety of PCA in elderly, Santangelo, E., *et al.*, (*ESA*) A.206
Analgesics opioid, diamorphine, Diamorphine/bupivacaine mixture *vs* plain bupivacaine: a comparison of epidural infusions in labour, Bailey, C. R., *et al.*, (*ESA*) A.169
Analgesics opioid, fentanyl, A comparison of midazolam and midazolam plus fentanyl for colonoscopy, Dupont, H., *et al.*, (*ESA*) A.9
——, Effects of intrathecal meperidine (MP), fentanyl (FN) and lidocaine (LD) on somatosensory (SSEP) and cortical motor (CMEP) evoked potentials in humans, Fernandez, S., *et al.*, (*ESA*) A.119
——, Fentanyl, as pethidine, inhibits post anaesthesia shivering, Alfonsi, P., *et al.*, (*ESA*) A.74
——, Fentanyl or buprenorphine side effects in spinal anaesthesia, Foppoli, R, *et al.*, (*ESA*) A.132
——, Intranasal fentanyl for breakthrough cancer pain or incident pain, Striebel, W. H., *et al.*, (*ESA*) A.210
——, Intranasal fentanyl for postoperative pain management in an unselected population, Striebel, W. H., *et al.*, (*ESA*) A.209
——, Pharmacokinetics of intranasal fentanyl, Striebel, H. W., *et al.*, (*ESA*) A.208
——, Propofol/fentanyl-anesthesia in patients with highly depressed cardiac function, Rauch, H., *et al.*, (*ESA*) A.30
——, Subarachnoid anaesthesia (SAA) and postoperative analgesia with bupivacaine (BV) plus fentanyl (FN) in geriatric patients, Fernandez, D., *et al.*, (*ESA*) A.131
Analgesics opioid, morphine, Addition of droperidol to PCA morphine: what is the optimal dose? Lamond, C. T., *et al.*, (*ESA*) A.204
——, Analgesia by wound infiltration before or after surgery in inguinal hernioraphy, Hennart, D., *et al.*, (*ESA*) A.202
——, Effect of morphine on a nociceptive flexion reflex in patients with postoperative pain, Chauvin, M., *et al.*, (*ESA*) A.115
——, High dose oral morphine in cancer pain management, Radbruch, L., *et al.*, (*ESA*) A.212
——, Intrathecal pain relief in terminally ill cancer patients at home, Wagemans, M. F. M., *et al.*, (*ESA*) A.213
——, Involvement of μ, δ, and κ receptors in the inhibition by intrathecal morphine of a C-fibre evoked reflex in the rat, Guirimand, F., *et al.*, (*ESA*) A.116
——, Postoperative analgesia: a two dosage regimens trial for i.m. morphine after early i.v. titration, Butscher, K., *et al.*, (*ESA*) A.201
——, Postoperative hypoxaemia: comparison of epidural and patient controlled analgesia, Spencer, A., *et al.*, (*ESA*) A.207
——, Preemptive analgesia with epidural morphine, Nègre, I., *et al.*, (*ESA*) A.203
——, Safety of PCA in elderly, Santangelo, E., *et al.*, (*ESA*) A.206
——, The effect of parenteral diclofenac and morphine on efficacy duration and height of blockade during continuous epidural bupivacaine 0.5%, Forbes, D., *et al.*, (*ESA*) A.125
——, Treatment of cancer pain with morphine (MO)—A double blind study of extradural (ED) *versus* intramuscular (im) routes of administration, Nath, S., *et al.*, (*ESA*) A.211
Analgesics opioid, pethidine, Effects of intrathecal meperidine (MP), fentanyl (FN) and lidocaine (LD) on somatosensory (SSEP) and cortical motor (CMEP) evoked potentials in humans, Fernandez, S., *et al.*, (*ESA*) A.119
——, Fentanyl, as pethidine, inhibits post anaesthesia shivering, Alfonsi, P., *et al.*, (*ESA*) A.74
——, Propofol anaesthesia with spontaneous breathing for extracorporeal shock wave lithotripsy, Pasch, T., *et al.*, (*ESA*) A.153
Analgesics opioid, sufentanil, Echocardiographic study of the induction with a low-dose of sufentanil for coronary artery surgery, Bromberg, N., *et al.*, (*ESA*) A.28
——, Patient controlled epidural analgesia *vs* intermittent injections during labor using 0.125% bupivacaine and sufentanil, Baudot, J., *et al.*, (*ESA*) A.170
——, Sufentanil first-pass pulmonary uptake at three different steady state concentrations of the drug, Boer, F., *et al.*, (*ESA*) A.147
——, Sufentanil increases intracranial pressure in patients with head trauma, Albanese, J., *et al.*, (*ESA*) A.107
Antacids, metoclopramide, Comparison of ondansetron, metoclopramide and droperidol for the prophylaxis of emetic symptoms after gynecological laparoscopic procedures, Geiger, C., *et al.*, (*ESA*) A.14
Antagonists benzodiazepine, flumazenil, Flumazenil facilitates intraoperative arousal in scoliosis surgery, Koscielniak-Nielsen, Z. J., *et al.*, (*ESA*) A.157
Antagonists benzodiazepine, Ro 15-4513, Nitrous oxide induced neuronal depression: modification through benzodiazepine receptors, Dzoljic, M., *et al.*, (*ESA*) A.112
Antagonists miscellaneous, Comparison of ondansetron, metoclopramide and droperidol for the prophylaxis of emetic symptoms after gynecological laparoscopic procedures, Geiger, C., *et al.*, (*ESA*) A.14
——, Double-blind comparison of ondansetron, droperidol and saline for prevention of nausea & vomiting after orthopaedic surgery, Gan, T. J., *et al.*, (*ESA*) A.13
——, Ondansetron 4 mg *vs* droperidol 1.25 mg in the prophylaxis of postoperative nausea and vomiting after alfentanil-supplemented inhalation anaesthesia, Alon, E., *et al.*, (*ESA*) A.12

Antagonists neuromuscular block, neostigmine, Neostigmine antagonism of neuromuscular blockade induced by mivacurium, vecuronium and atracurium, Dernovoi, B. S., *et al.*, (*ESA*) A.137

——, Reversal of vecuronium induced neuromuscular blockade: No effects of atropine administration timing, Baurain, M. J., *et al.*, (*ESA*) A.134

Antagonists opioid, miscellaneous, Differential effects of specific delta and kappa opioid antagonists on the bidirectionnal effect of naloxone in arthritic rats, Cattaneo, I., *et al.*, (*ESA*) A.114

——, Involvement of μ, δ, and κ receptors in the inhibition by intrathecal morphine of a C-fibre evoked reflex in the rat, Guirimand, F., *et al.*, (*ESA*) A.116

Antagonists opioid, naloxone, Differential effects of specific delta and kappa opioid antagonists on the bidirectionnal effect of naloxone in arthritic rats, Cattaneo, I., *et al.*, (*ESA*) A.114

Antibiotics, External ventricular CSF drains infections, Mahé, V., *et al.*, (*ESA*) A.109

Arterial pressure, drug effects, Mechanisms of ECG changes during caesarean section (CS)—a hypothesis, Svanström, M., *et al.*, (*ESA*) A.177

Arterial pressure, measurement, Clinical evaluation of the calibration of noninvasive continuous blood pressure measurement devices by means of oscillometric blood pressure measurements, de Jong, J. R., *et al.*, (*ESA*) A.15

Blood, anaesthetic concentration, Determination of a pharmacokinetic model for propofol induction of anaesthesia, Viviand, X., *et al.*, (*ESA*) A.150

——, Target-controlled intravenous sedation with propofol, Mergaert, C., *et al.*, (*ESA*) A.149

Blood, anticoagulants, aspirin, Inhibition of increase of blood thromboxane concentration by acetylsalicylic acid after release of tourniquet in lower extremity operations, Ojanen, R., *et al.*, (*ESA*) A.94

Blood, coagulation, Aprotinin does not decrease surgical bleeding and could promote arterial thrombosis in the pig: A prospective randomized, blind, study, Samama, C. M., *et al.*, (*ESA*) A.100

——, Blood requirements reduction in orthotopic liver transplantation with aprotinin, Monedero, P., *et al.*, (*ESA*) A.98

——, High dose aprotinin *versus* desmo-pressin acetate treatment in cardiac surgery, Hidalgo, F., *et al.*, (*ESA*) A.99

——, The combined prophylactic administration of H1 and H2 receptor blockers in the prevention of protamine related haemodynamic effects and the relation between antihistaminics-leucocytes and pulmonary vascular resistance, Durak, P., *et al.*, (*ESA*) A.95

——, The relationship between cardiopulmonary bypass related immunologic effects and complement, thromboxane and leucocyte parameters, Durak, P., *et al.*, (*ESA*) A.96

——, Use of aprotinine during cytoreductive surgery of ovarian cancer, Lequeau, F., *et al.*, (*ESA*) A.97

Blood, glucose, Neonatal glycemia: does the maternal i.v. fluid regimen during labor make a difference? Menigaux, C., *et al.*, (*ESA*) A.175

Blood, haematopoiesis, Effects of recombinant-human erythropoietin on postoperative transfusion requirements in subjects undergoing major orthopaedic surgery, Faris, P. P., *et al.*, (*ESA*) A.101

Blood, leucocytes, Effects of diazepam additives on the mononuclear phagocytic system, Catalá, J. C., *et al.*, (*ESA*) A.89

——, The combined prophylactic administration of H1 and H2 receptor blockers in the prevention of protamine related haemodynamic effects and the relation between antihistaminics-leucocytes and pulmonary vascular resistance, Durak, P., *et al.*, (*ESA*) A.95

——, The relationship between cardiopulmonary bypass related immunologic effects and complement, thromboxane and leucocyte parameters, Durak, P., *et al.*, (*ESA*) A.96

Blood, loss, Aprotinin does not decrease surgical bleeding and could promote arterial thrombosis in the pig: A prospective randomized, blind, study, Samama, C. M., *et al.*, (*ESA*) A.100

——, Blood requirements reduction in orthotopic liver transplantation with aprotinin, Monedero, P., *et al.*, (*ESA*) A.98

——, High dose aprotinin *versus* desmo-pressin acetate treatment in cardiac surgery, Hidalgo, F., *et al.*, (*ESA*) A.99

——, The effects of bupivacaine, mepivacaine and prilocaine on platelet aggregation, Bayhan, N., *et al.*, (*ESA*) A.123

——, Use of aprotinine during cytoreductive surgery of ovarian cancer, Lequeau, F., *et al.*, (*ESA*) A.97

Blood, platelets, Acute preoperative plasmapheresis during cardiac surgery, Armellin, G., *et al.*, (*ESA*) A.104

——, The effects of bupivacaine, mepivacaine and prilocaine on platelet aggregation, Bayhan, N., *et al.*, (*ESA*) A.123

Blood, replacement, Acute preoperative plasmapheresis during cardiac surgery, Armellin, G., *et al.*, (*ESA*) A.104

——, Blood requirements reduction in orthotopic liver transplantation with aprotinin, Monedero, P., *et al.*, (*ESA*) A.98

——, Effects of plasma volume substitution on right ventricle volumes and function using Elohes® and Plasmion®, Lepage, J. Y., *et al.*, (*ESA*) A.35

——, Effects of recombinant-human erythropoietin on postoperative transfusion requirements in subjects undergoing major orthopaedic surgery, Faris, P. P., *et al.*, (*ESA*) A.101

——, High dose aprotinin *versus* desmo-pressin acetate treatment in cardiac surgery, Hidalgo, F., *et al.*, (*ESA*) A.99

——, Preoperative autotransfusion in emergency surgery for spine trauma, Riou, B., *et al.*, (*ESA*) A.102

Blood, salvage, Acute preoperative plasmapheresis during cardiac surgery, Armellin, G., *et al.*, (*ESA*) A.104

——, Effects of postoperative auto-transfusion in spine surgery, Riou, B., *et al.*, (*ESA*) A.103

——, Preoperative autotransfusion in emergency surgery for spine trauma, Riou, B., *et al.*, (*ESA*) A.102

Blood, volume, A comparison between various hemodynamic parameters reflecting preload during traded hemorrhage in ventilated dogs, Preisman, S., *et al.*, (*ESA*) A.51

——, Effects of plasma volume substitution on right ventricle volumes and function using Elohes® and Plasmion®, Lepage, J. Y., *et al.*, (*ESA*) A.35

——, Glycine and its metabolites during and after intrauterine YAG laser surgery, Van Boven, M. J., *et al.*, (*ESA*) A.87

——, Prevention of acute tubular necrosis by volume loading in kidney transplantation, Mouquet, C., *et al.*, (*ESA*) A.82

——, Propofol/fentanyl-anesthesia in patients with highly depressed cardiac function, Rauch, H., *et al.*, (*ESA*) A.30

——, The systolic pressure variation predicts response to volume loading in patients ventilated after aortic surgery, Coriat, P., *et al.*, (*ESA*) A.38

——, Volume loading and hormonal factors in the prevention of acute tubular necrosis in kidney transplantation, Mouquet, C., *et al.*, (*ESA*) A.83

Brain, blood flow, Cerebral blood flow velocities (CBFV) during anaesthesia for gynaecological laparoscopic surgery, Granry, J. C., *et al.*, (*ESA*) A.32

——, Cerebral perfusion during obstructive sleep apnea (OSA), Bålfors, E., *et al.*, (*ESA*) A.62

——, EEG-monitoring during defibrillator-implantation: effects of repetitive cerebral ischemia on electric brain activity, Spies, C., *et al.*, (*ESA*) A.110

——, Midazolam prevents ketamine-induced stimulation of cerebral metabolism, Åkeson, J., *et al.*, (*ESA*) A.111

——, Sufentanil increases intracranial pressure in patients with head trauma, Albanese, J., *et al.*, (*ESA*) A.107

——, The choice of ECM rate could improve the neuroprotection during CPR, Iannuzzi, E., *et al.*, (*ESA*) A.195

——, Transcranial Doppler sonography: effect of propofol and thiopental in patients with brain tumors and brain injuries, Schregel, W., *et al.*, (*ESA*) A.105

Brain, electroencephalography, EEG-monitoring during defibrillator-implantation: effects of repetitive cerebral ischemia on electric brain activity, Spies, C., *et al.*, (*ESA*) A.110

Brain, evoked potentials, Accuracy of processed auditory evoked response in predicting movement during cardiac surgery, Kuppe, H., *et al.*, (*ESA*) A.31

——, Effects of intrathecal meperidine (MP), fentanyl (FN) and lidocaine (LD) on somatosensory (SSEP) and cortical motor (CMEP) evoked potentials in humans, Fernandez, S., *et al.*, (*ESA*) A.119

——, Nitrous oxide induced neuronal depression: modification through benzodiazepine receptors, Dzoljic, M., *et al.*, (*ESA*) A.112

Brain, GABA, Dexmedetomidine does not exercise its anesthetic action through GABA, Salonen, M., *et al.*, (*ESA*) A.113

Brain, injury, Transcranial Doppler sonography: effect of propofol and thiopental in patients with brain tumors and brain injuries, Schregel, W., *et al.*, (*ESA*) A.105

Brain, intracranial pressure, Effect of esmolol *versus* lidocaine on intracranial pressure and haemodynamic responses to laryngoscopy and intubation, Samaha, T., *et al.*, (*ESA*) A.118

——, Jugular bulb metabolic monitoring during hyperventilation in severe head trauma patients, De Deyne, C., *et al.*, (*ESA*) A.106

——, Sufentanil increases intracranial pressure in patients with head trauma, Albanese, J., *et al.*, (*ESA*) A.107

Brain, ischaemia, EEG-monitoring during defibrillator-implantation: effects of repetitive cerebral ischemia on electric brain activity, Spies, C., *et al.*, (*ESA*) A.110

——, Jugular bulb metabolic monitoring during hyperventilation in severe head trauma patients, De Deyne, C., *et al.*, (*ESA*) A.106

Brain, metabolism, Midazolam prevents ketamine-induced stimulation of cerebral metabolism, Åkeson, J., *et al.*, (*ESA*) A.111

Brain, saccadic eye movements, Evaluation of saccadic eye movements as an objective test during recovery from anesthesia, Paut, O., *et al.*, (*ESA*) A.10

Burkitt's lymphoma, Is Burkitt's lymphoma an etiology or a differential diagnosis of malignant hyperthermia? Lienhart, A., *et al.*, (*ESA*) A.93

Calcium channel block, nicardipine, Does nicardipine potentiate the neuromuscular block of atracurium? Bazin, J. E., *et al.*, (*ESA*) A.136

Calcium channel block, nifedipine, Effect of premedication with nifedipine on intraoperative hypothermia, Vassilieff, N., *et al.*, (*ESA*) A.71

Cancer, High dose oral morphine in cancer pain management, Radbruch, L., *et al.*, (*ESA*) A.212

——, Intranasal fentanyl for breakthrough cancer pain or incident pain, Striebel, W. H., *et al.*, (*ESA*) A.210

——, Intrathecal pain relief in terminally ill cancer patients at home, Wagemans, M. F. M., *et al.*, (*ESA*) A.213

——, Is Burkitt's lymphoma an etiology or a differential diagnosis of malignant hyperthermia? Lienhart, A., *et al.*, (*ESA*) A.93

——, Postoperative hypoxaemia: comparison of epidural and patient controlled analgesia, Spencer, A., *et al.*, (*ESA*) A.207

——, Transcranial Doppler sonography: effect of propofol and thiopental in patients with brain tumors and brain injuries, Schregel, W., *et al.*, (*ESA*) A.105

——, Treatment of cancer pain with morphine (MO)—A double blind study of extradural (ED) *versus* intramuscular (im) routes of administration, Nath, S., *et al.*, (*ESA*) 211–A

——, Use of aprotinine during cytoreductive surgery of ovarian cancer, Lequeau, F., *et al.*, (*ESA*) A.97

Carbon dioxide, measurement, Relationship between arterial $P\mathrm{co}_2$ (Pa_{CO_2}) and end tidal CO_2 (ETco_2) recorded through a laryngeal mask (LMA) in children breathing spontaneously, Van Obbergh, L. J., *et al.*, (*ESA*) A.164

Carbon dioxide, partial pressure, Is correlation of arterial and end-tidal carbon dioxide pressure during inhalation anaesthesia better with laryngeal mask as compared to face mask? Ivens, D., *et al.*, (*ESA*) A.17

——, Relationship between arterial $P\mathrm{co}_2$ (Pa_{CO_2}) and end tidal CO_2 (ETco_2) recorded through a laryngeal mask (LMA) in children breathing spontaneously, Van Obbergh, L. J., *et al.*, (*ESA*) A.164

——, Respiratory effects of laparoscopic cholecystectomy (preliminary data), Crea, M. A., *et al.*, (*ESA*) A.63

Cardiorespiratory system, effects, Abdominal wall retraction may decrease anaesthesiological risks of laparoscopic cholecystectomy, Vereczkey, Z., *et al.*, (*ESA*) A.64

——, Diaphragmatic function after bupivacaine cervical extradural analgesia for chronic pain therapy, Nyström, E., *et al.*, (*ESA*) A.65

——, Pulmonary and systemic vascular effects of isoproterenol, nitroglycerin and prostaglandin E1 early after cardiac operations in patients with pulmonary hypertension, Alvarez, J., *et al.*, (*ESA*) A.27

——, Respiratory effects of laparoscopic cholecystectomy (preliminary data), Crea, M. A., *et al.*, (*ESA*) A.63

——, The combined prophylactic administration of H1 and H2 receptor blockers in the prevention of protamine related haemodynamic effects and the relation between antihistaminics-leucocytes and pulmonary vascular resistance, Durak, P., *et al.*, (*ESA*) A.95

Cardiovascular system, effects, Does exogenous dopamine reverse cardiovascular depression induced by isoflurane during thoracic epidural blockade? Raner, C., *et al.*, (*ESA*) A.49

——, Effects of nitrous oxide (N_2O) on systemic haemodynamics, regional left ventricular (LV) function and incidence of myocardial ischaemia (MI) in vascular surgical patients with coronary artery disease (CAD), Hohner, P., *et al.*, (*ESA*) A.41

——, Local *versus* neurogenic vasodilator effects of desflurane and isoflurane in the small intestine, Sundeman, H., *et al.*, (*ESA*) A.50

Cardiovascular system, responses, Comparison of dobutamine with enoximone following open heart surgery in small children, Innes, P., *et al.*, (*ESA*) A.167

——, Dose dependent effects of oral medication with midazolam, Biro, P., *et al.*, (*ESA*) A.156

——, Echocardiographic study of the induction with a low-dose of sufentanil for coronary artery surgery, Bromberg, N., *et al.*, (*ESA*) A.28

——, Effect of esmolol *versus* lidocaine on intracranial pressure and haemodynamic responses to laryngoscopy and intubation, Samaha, T., *et al.*, (*ESA*) A.118

——, Effects of oral preoperative guanfacine on anesthetics requirements, Engelman, E., *et al.*, (*ESA*) A.144

——, Evaluation of cardiac function in ICU: right heart catheterization *vs* transesophageal echocardiography. Preliminary results, Vivien, B., *et al.*, (*ESA*) A.183

——, Influence of pneumoperitoneum and posture on hemodynamic and stress responses during anaesthesia for laparoscopic surgery, Odeberg, S., *et al.*, (*ESA*) A.34

——, Prevention of acute tubular necrosis by volume loading in kidney transplantation, Mouquet, C., *et al.*, (*ESA*) A.82

——, Tolerance of preoperative transesophageal echocardiography in patients scheduled for aortic surgery, Gosgnach, M., *et al.*, (*ESA*) A.21

Cat, Local *versus* neurogenic vasodilator effects of desflurane and isoflurane in the small intestine, Sundeman, H., *et al.*, (*ESA*) A.50

Cerebrospinal fluid, External ventricular CSF drains infections, Mahé, V., *et al.*, (*ESA*) A.109

Children, Clonidine in paediatric caudal anaesthesia, Jamali, S., *et al.*, (*ESA*) A.160

——, Comparison of dobutamine with enoximone following open heart surgery in small children, Innes, P., *et al.*, (*ESA*) A.167

——, Continuous monitoring of Sp_{O_2} during total intravenous anaesthesia with ketamine and spontaneous ventilation, Joly, L.-M., *et al.*, (*ESA*) A.58

——, Evaluation of the efficacy of forced-air warmer (Bair Hugger) during spinal surgery in children, Murat, I., *et al.*, (*ESA*) A.165

——, Neuromuscular blockade following mivacurium in children during N_2O–halothane, Orliaguet, G., *et al.*, (*ESA*) A.163

——, Propofol for tracheal intubation in paediatric outpatient anaesthesia, Montasser, A. M., (*ESA*) A.161

——, Relationship between arterial $P\mathrm{co}_2$ (Pa_{CO_2}) and end tidal CO_2 (ETco_2) recorded through a laryngeal mask (LMA) in children breathing spontaneously, Van Obbergh, L. J., *et al.*, (*ESA*) A.164

——, The pharmacokinetics of rocuronium in pediatric patients: a pooled data analysis, Meistelman, C., *et al.*, (*ESA*) A.138

——, Use of thoracic epidural block for perioperative analgesia in children, Entress, A. H., *et al.*, (*ESA*) A.158

Complications, accidents, Evaluation of systematic TEE in patients suspected of blunt chest trauma, Catoire, P., *et al.*, (*ESA*) A.192

——, Jugular bulb metabolic monitoring during hyperventilation in severe head trauma patients, De Deyne, C., *et al.*, (*ESA*) A.106

——, Sufentanil increases intracranial pressure in patients with head trauma, Albanese, J., *et al.*, (*ESA*) A.107

——, The part of rescue helicopters in large accidents and disasters, Wenker, O., (*ESA*) A.197

Complications, adult respiratory distress syndrome, Histology aspects of pulmonary barotrauma in critically ill patients with acute respiratory failure, Rouby, J. J., *et al.*, (*ESA*) A.181

——, Non invasive monitoring of CO_2 in patients with septic shock, Bodin, L., *et al.*, (*ESA*) A.191

Complications, alcohol abuse, Carbohydrate deficient transferrin: a new copredictor of alcoholism related postoperative complications? Heil, T., *et al.*, (*ESA*) A.88

Complications, aneurysm, Cardiac function in aneurysmal subarachnoid haemorrhage, Moulay, N., *et al.*, (*ESA*) A.108

——, Helicopter transportation of patients with symptomatic aortic aneurysms, Fellerter, P., *et al.*, (*ESA*) A.196

Complications, aortic rupture, Diagnosis of aortic rupture by transesophageal echocardiography (TEE), Goarin, J. P., *et al.*, (*ESA*) A.193

Complications, arthritis, Differential effects of specific delta and kappa opioid antagonists on the bidirectionnal effect of naloxone in arthritic rats, Cattaneo, I., *et al.*, (*ESA*) A.114

Complications, atelectasis, Recruitment of atelectasis during general anaesthesia: a CT-study, Rothen, H. U., *et al.*, (*ESA*) A.53

Complications, barotrauma, Histology aspects of pulmonary barotrauma in critically ill patients with acute respiratory failure, Rouby, J. J., *et al.*, (*ESA*) A.181

Complications, Burkitt's lymphoma, Is Burkitt's lymphoma an etiology or a differential diagnosis of malignant hyperthermia? Lienhart, A., *et al.*, (*ESA*) A.93

Complications, colitis, Measurement of sigmoid intramural pH during orthotopic liver transplantation, Auroy, Y., *et al.*, (*ESA*) A.76

Complications, death, A national database for intensive care medicine in Sweden, Karling, M., (*ESA*) A.8

Complications, embolism, Inhibition of increase of blood thromboxane concentration by acetylsalicylic acid after release of tourniquet in lower extremity operations, Ojanen, R., *et al.*, (*ESA*) A.94

——, Reassessment of bronchoalveolar lavage in the diagnosis of post traumatic pulmonary fat embolism, Mimoz, O., *et al.*, (*ESA*) A.180

——, Systemic gas embolism in pulmonary contusion diagnosed by transesophageal echocardiography, Saada, M., *et al.*, (*ESA*) A.194

Complications, endocardial endothelium damage, Endocardial endothelium modulates *in vivo* left ventricular performance, De Hert, S. G., *et al.*, (*ESA*) A.47

Complications, haemorrhage, Cardiac function in aneurysmal subarachnoid haemorrhage, Moulay, N., *et al.*, (*ESA*) A.108

Complications, head injury, Jugular bulb metabolic monitoring during hyperventilation in severe head trauma patients, De Deyne, C., *et al.*, (*ESA*) A.106

——, Sufentanil increases intracranial pressure in patients with head trauma, Albanese, J., *et al.*, (*ESA*) A.107

Complications, headache, Best Quincke point needle for Caesarean section, Lyons, G., (*ESA*) A.174

——, Epidural blood patch for treatment of postdural puncture headache, Rosenberg, P. H., *et al.*, (*ESA*) A.129

——, Headache—new needles and spinal anaesthesia for C. section, Thormann, F., *et al.*, (*ESA*) A.173

——, Incidence of post dural puncture headache in young adults by the use of the Sprôtte needle: 300 patients, Descraques, C., *et al.*, (*ESA*) A.127

——, Nine years of clinical experience with 29 gauge spinal needles, Dittmann, M., *et al.*, (*ESA*) A.126

——, Postdural puncture headaches are not related to the duration of spinal catheter placement, Liu, N., *et al.*, (*ESA*) A.128

Complications, hypertension, Is the vasoconstrictive effect of cyclosporine mediated by endothelin in kidney transplantation? Mouquet, C., *et al.*, (*ESA*) A.84

Complications, hyperthermia, Exercise and malignant hyperthermia: family investigations, Kozak Ribbens, G., *et al.*, (*ESA*) A.92

——, Is Burkitt's lymphoma an etiology or a differential diagnosis of malignant hyperthermia? Lienhart, A., *et al.*, (*ESA*) A.93

Complications, hypoglycaemia, Neonatal glycemia: does the maternal i.v. fluid regimen during labor make a difference? Menigaux, C., *et al.*, (*ESA*) A.175

Complications, hypotension, Influence of chronic angiotensin converting enzyme inhibition on systolic pressure variation during anesthetic induction, Puybasset, L., *et al.*, (*ESA*) A.39

——, Ketamine does not prevent hypotension caused by induction of anaesthesia with propofol in elderly patients, Blockmans, D., *et al.*, (*ESA*) A.40

——, Mechanisms of ECG changes during caesarean section (CS)—a hypothesis, Svanström, M., *et al.*, (*ESA*) A.177

——, Spinal anesthesia for C section: addition of phenylephrine to ephedrine for prevention of maternal hypotension, Thirion, A.-V., *et al.*, (*ESA*) A.172

Complications, hypothermia, An investigation into the effect of passive and active cutaneous warming devices on intraoperative body temperature in elderly patients, Bennet, J., *et al.*, (*ESA*) A.73

——, Effect of premedication with nifedipine on intraoperative hypothermia, Vassilieff, N., *et al.*, (*ESA*) A.71

——, Evaluation of the efficacy of forced-air warmer (Bair Hugger) during spinal surgery in children, Murat, I., *et al.*, (*ESA*) A.165

——, Preoperative skin-surface warming reduces intraoperative hypothermia, Camus, Y., *et al.*, (*ESA*) A.72

Complications, hypovolaemia, A comparison between various hemodynamic parameters reflecting preload during traded hemorrhage in ventilated dogs, Preisman, S., *et al.*, (*ESA*) A.51

——, Determinants of systolic pressure variation in patients ventilated after vascular surgery, Beaussier, M., *et al.*, (*ESA*) A.37

——, Effects of plasma volume substitution on right ventricle volumes and function using Elohes® and Plasmion®, Lepage, J. Y., *et al.*, (*ESA*) A.35

——, Evaluation of cardiac function in ICU: right heart catheterization *vs* transesophageal echocardiography. Preliminary results, Vivien, B., *et al.*, (*ESA*) A.183

——, Influence of chronic angiotensin converting enzyme inhibition on systolic pressure variation during anesthetic induction, Puybasset, L., *et al.*, (*ESA*) A.39

——, The systolic pressure variation predicts response to volume loading in patients ventilated after aortic surgery, Coriat, P., *et al.*, (*ESA*) A.38

Complications, hypoxaemia, Continuous monitoring of Sp_{O_2} during total intravenous anaesthesia with ketamine and spontaneous ventilation, Joly, L.-M., *et al.*, (*ESA*) A.58

——, Hypoxic events after general anaesthesia in the recovery room, Degasperi, D., *et al.*, (*ESA*) A.59

——, Influence of anaesthesia on post-operative hypoxaemia, Georgiou, L., *et al.*, (*ESA*) A.60

——, Postoperative hypoxaemia: comparison of epidural and patient controlled analgesia, Spencer, A., *et al.*, (*ESA*) A.207

Complications, infections, External ventricular CSF drains infections, Mahé, V., *et al.*, (*ESA*) A.109

Complications, myocardial infarction, Effects of nitrous oxide (N_2O) on systemic haemodynamics, regional left ventricular (LV) function and incidence of myocardial ischaemia (MI) in vascular surgical patients with coronary artery disease (CAD), Hohner, P., *et al.*, (*ESA*) A.41

Complications, myolysis, Exercise and malignant hyperthermia: family investigations, Kozak Ribbens, G., *et al.*, (*ESA*) A.92

Complications, neurological, Flumazenil facilitates intraoperative arousal in scoliosis surgery, Koscielniak-Nielsen, Z. J., *et al.*, (*ESA*) A.157

Complications, obesity, The respiratory compliance in normal and obese subjects during anaesthesia, Mulazzi, D., *et al.*, (*ESA*) A.54

Complications, osteoarthrosis, Diaphragmatic function after bupivacaine cervical extradural analgesia for chronic pain therapy, Nyström, E., *et al.*, (*ESA*) A.65

Complications, pulmonary, Reassessment of bronchoalveolar lavage in the diagnosis of post traumatic pulmonary fat embolism, Mimoz, O., *et al.*, (*ESA*) A.180

——, Septic shock: effect of a goal-directed therapy on oxygen metabolism and serum cytokine levels, Martin, C., *et al.*, (*ESA*) A.189

Complications, renal, Outcome for patients in intensive care with acute renal failure requiring dialysis, Ejlersen, E., *et al.*, (*ESA*) A.7

——, Prevention of acute tubular necrosis by volume loading in kidney transplantation, Mouquet, C., *et al.*, (*ESA*) A.82

——, Volume loading and hormonal factors in the prevention of acute tubular necrosis in kidney transplantation, Mouquet, C., *et al.*, (*ESA*) A.83

Complications, respiratory, Continuous spirometry: an aid in the intraoperative respiratory monitoring—case reports, Bardoczky, G., *et al.*, (*ESA*) A.55

Complications, respiratory depression, A comparison of midazolam and midazolam plus fentanyl for colonoscopy, Dupont, H., *et al.*, (*ESA*) A.9

Complications, septicaemia, Comparison of two therapeutic strategies of septic shock, Martin, C., *et al.*, (*ESA*) A.190

——, Influence of N-acetylcysteine on O_2 consumption and gastric intramucosal pH in septic patients, Spies, C., *et al.*, (*ESA*) A.186

——, Influence of norepinephrine therapy on the oxygen supply and lactate extraction rate of the liver in the septic pig, Schäfer, R., *et al.*, (*ESA*) A.184

——, Molecular mediators and post-bacteraemic phase, Martínez Urionabarrenetxea, K., *et al.*, (*ESA*) A.187

——, Non invasive monitoring of CO_2 in patients with septic shock, Bodin, L., *et al.*, (*ESA*) A.191

——, Septic shock: effect of a goal-directed therapy on oxygen metabolism and serum cytokine levels, Martin, C., *et al.*, (*ESA*) A.189

——, The effect of dobutamine and norepinephrine on global and splanchnic O_2 consumption, Meier-Hellmann, A., *et al.*, (*ESA*) A.185

Complications, shivering, Fentanyl, as pethidine, inhibits post anaesthesia shivering, Alfonsi, P., *et al.*, (*ESA*) A.74

Complications, sinusitis, Incidence of bacterial maxillary sinusitis in critically ill patients with radiologic maxillary sinusitis, Bodin, L., *et al.*, (*ESA*) A.179

Complications, stenosis, Dipyridamole-TEE and 24 h Holter-ECG as preoperative screening tests for coronary artery disease in patients with abdominal aortic aneurysm, Östman, M., *et al.*, (*ESA*) A.22

——, Does routine preoperative coronary angiography modify outcome after aortic surgery? Gosgnach, M., *et al.*, (*ESA*) A.6
——, Evaluation of haemodynamic indices of myocardial ischaemia in patients with coronary artery disease (CAD), Hohner, P., *et al.*, (*ESA*) A.23
——, Indications for coronary revascularisation in vascular surgical patients, Gosgnach, M., *et al.*, (*ESA*) A.5
——, Pulmonary and systemic vascular effects of isoproterenol, nitroglycerin and prostaglandin E1 early after cardiac operations in patients with pulmonary hypertension, Alvarez, J., *et al.*, (*ESA*) A.27
——, Sensitivity and specificity of mechanical and electrocardiographic myocardial ischaemia (MI) monitoring techniques, Hohner, P., *et al.*, (*ESA*) A.26
——, The use of the CUSUM plot for determination of myocardial ischaemia threshold during atrial pacing in patients with coronary artery disease, Reiz, S., *et al.*, (*ESA*) A.24
Complications, thrombosis, Aprotinin does not decrease surgical bleeding and could promote arterial thrombosis in the pig: A prospective randomized, blind, study, Samama, C. M., *et al.*, (*ESA*) A.100
——, Inhibition of increase of blood thromboxane concentration by acetylsalicylic acid after release of tourniquet in lower extremity operations, Ojanen, R., *et al.*, (*ESA*) A.94
Complications, trauma, Diagnosis of aortic rupture by transesophageal echocardiography (TEE), Goarin, J. P., *et al.*, (*ESA*) A.193
——, Evaluation of systematic TEE in patients suspected of blunt chest trauma, Catoire, P., *et al.*, (*ESA*) A.192
——, Jugular bulb metabolic monitoring during hyperventilation in severe head trauma patients, De Deyne, C., *et al.*, (*ESA*) A.106
——, Reassessment of bronchoalveolar lavage in the diagnosis of post traumatic pulmonary fat embolism, Mimoz, O., *et al.*, (*ESA*) A.180
——, Sufentanil increases intracranial pressure in patients with head trauma, Albanese, J., *et al.*, (*ESA*) A.107
——, Systemic gas embolism in pulmonary contusion diagnosed by transesophageal echocardiography, Saada, M., *et al.*, (*ESA*) A.194
Complications, ultrasound, Endocardial endothelium modulates *in vivo* left ventricular performance, De Hert, S. G., *et al.*, (*ESA*) A.47
Computers, A national database for intensive care medicine in Sweden, Karling, M., (*ESA*) A.8

Dog, A comparison between various hemodynamic parameters reflecting preload during traded hemorrhage in ventilated dogs, Preisman, S., *et al.*, (*ESA*) A.51
——, Does exogenous dopamine reverse cardiovascular depression induced by isoflurane during thoracic epidural blockade? Raner, C., *et al.*, (*ESA*) A.49
——, Endocardial endothelium modulates *in vivo* left ventricular performance, De Hert, S. G., *et al.*, (*ESA*) A.47
——, Lemakalim reverses ventricular conduction impairment induced by a large dose of bupivacaine in anesthetized dogs, de La Coussaye, J. E., *et al.*, (*ESA*) A.121
Donors, organ transplantation, Effects of desmopressin (DDAVP) supplementation in brain dead organ donors (BDOD) on early recipient renal function, Guesde, R., *et al.*, (*ESA*) A.79
——, Fiberoptic bronchoscopy in brain dead organ donors, Riou, B., *et al.*, (*ESA*) A.80
Drug delivery, Blended anaesthesia in pediatric major surgery: top-up *vs* epidural continuous infusion, Savoia, G., *et al.*, (*ESA*) A.159
——, Treatment of cancer pain with morphine (MO)—A double blind study of extradural (ED) *versus* intramuscular (im) routes of administration, Nath, S., *et al.*, (*ESA*) 211–A
Drug delivery, computerized, Computer-controlled syringe pump improves safety of pharmacokinetic models, Duranteau, R., *et al.*, (*ESA*) A.148
——, Determination of a pharmacokinetic model for propofol induction of anaesthesia, Viviand, X., *et al.*, (*ESA*) A.150
——, Target-controlled intravenous sedation with propofol, Mergaert, C., *et al.*, (*ESA*) A.149
Drug delivery, nasal, Intranasal fentanyl for breakthrough cancer pain or incident pain, Striebel, W. H., *et al.*, (*ESA*) A.210
——, Intranasal fentanyl for postoperative pain management in an unselected population, Striebel, W. H., *et al.*, (*ESA*) A.209
——, Pharmacokinetics of intranasal fentanyl, Striebel, H. W., *et al.*, (*ESA*) A.208
Drug delivery, oral, Dose dependent effects of oral medication with midazolam, Biro, P., *et al.*, (*ESA*) A.156
——, High dose oral morphine in cancer pain management, Radbruch, L., *et al.*, (*ESA*) A.212
Drug delivery, transdermal, Pharmacokinetic behaviour of transdermal fentanyl, Van Bastelaere, M., *et al.*, (*ESA*) A.146

Education, junior staff, Nine years of clinical experience with 29 gauge spinal needles, Dittmann, M., *et al.*, (*ESA*) A.126
Embolism, air, Systemic gas embolism in pulmonary contusion diagnosed by transesophageal echocardiography, Saada, M., *et al.*, (*ESA*) A.194
Embolism, fat, Reassessment of bronchoalveolar lavage in the diagnosis of post traumatic pulmonary fat embolism, Mimoz, O., *et al.*, (*ESA*) A.180
Enzymes, angiotensin converting, inhibition, Does captopril modify the arterial response to vasopressor substances? Le Pelley, E., *et al.*, (*ESA*) A.48
——, Influence of chronic angiotensin converting enzyme inhibition on systolic pressure variation during anesthetic induction, Puybasset, L., *et al.*, (*ESA*) A.39
Enzymes, creatine kinase, Cardiac function in aneurysmal subarachnoid haemorrhage, Moulay, N., *et al.*, (*ESA*) A.108
Equipment, airway, Is correlation of arterial and end-tidal carbon dioxide pressure during inhalation anaesthesia better with laryngeal mask as compared to face mask? Ivens, D., *et al.*, (*ESA*) A.17
——, Relationship between arterial $P\text{co}_2$ (Pa_{CO_2}) and end tidal CO_2 (ETco_2) recorded through a laryngeal mask (LMA) in children breathing spontaneously, Van Obbergh, L. J., *et al.*, (*ESA*) A.164
——, Ventilation with halothane is less affected in children with laryngeal mask airway than with endotracheal tube, Reignier, J., *et al.*, (*ESA*) A.162
Equipment, blankets, Preoperative skin-surface warming reduces intraoperative hypothermia, Camus, Y., *et al.*, (*ESA*) A.72
Equipment, blankets reflective, An investigation into the effect of passive and active cutaneous warming devices on intraoperative body temperature in elderly patients, Bennet, J., *et al.*, (*ESA*) A.73
Equipment, calibration, Clinical evaluation of the calibration of noninvasive continuous blood pressure measurement devices by means of oscillometric blood pressure measurements, de Jong, J. R., *et al.*, (*ESA*) A.15
Equipment, catheters subarachnoid, Postdural puncture headaches are not related to the duration of spinal catheter placement, Liu, N., *et al.*, (*ESA*) A.128
Equipment, Cell Saver, Preoperative autotransfusion in emergency surgery for spine trauma, Riou, B., *et al.*, (*ESA*) A.102
Equipment, computers, Computer-controlled syringe pump improves safety of pharmacokinetic models, Duranteau, R., *et al.*, (*ESA*) A.148
——, Determination of a pharmacokinetic model for propofol induction of anaesthesia, Viviand, X., *et al.*, (*ESA*) A.150
——, Target-controlled intravenous sedation with propofol, Mergaert, C., *et al.*, (*ESA*) A.149
Equipment, heat-moisture exchangers, Preservation of humidity and heat of respiratory gases in patients with minute ventilation > 10 l/min, Martin, C., *et al.*, (*ESA*) A.20
Equipment, helicopters, Helicopter transportation of patients with symptomatic aortic aneurysms, Felleiter, P., *et al.*, (*ESA*) A.196
——, The part of rescue helicopters in large accidents and disasters, Wenker, O., (*ESA*) A.197
Equipment, humidifiers, Effectiveness of core warming on net transfer of body heat across the skin, Kulkarni, P., *et al.*, (*ESA*) A.70
——, Preservation of humidity and heat of respiratory gases in patients with minute ventilation > 10 l/min, Martin, C., *et al.*, (*ESA*) A.20
Equipment, infusion systems, Computer-controlled syringe pump improves safety of pharmacokinetic models, Duranteau, R., *et al.*, (*ESA*) A.148
——, Determination of a pharmacokinetic model for propofol induction of anaesthesia, Viviand, X., *et al.*, (*ESA*) A.150
——, Target-controlled intravenous sedation with propofol, Mergaert, C., *et al.*, (*ESA*) A.149
Equipment, masks anaesthesia, Is correlation of arterial and end-tidal carbon dioxide pressure during inhalation anaesthesia better with laryngeal mask as compared to face mask? Ivens, D., *et al.*, (*ESA*) A.17
Equipment, needles, Best Quincke point needle for Caesarean section, Lyons, G., (*ESA*) A.174

——, Headache—new needles and spinal anaesthesia for C. section, Thormann, F., *et al.*, (*ESA*) A.173
——, Incidence of post dural puncture headache in young adults by the use of the Sprôtte needle: 300 patients, Descraques, C., *et al.*, (*ESA*) A.127
——, Nine years of clinical experience with 29 gauge spinal needles, Dittmann, M., *et al.*, (*ESA*) A.126
Equipment, retractors, Abdominal wall retraction may decrease anaesthesiological risks of laparoscopic cholecystectomy, Vereczkey, Z., *et al.*, (*ESA*) A.64
Equipment, sensors, Influence of posture on the respiratory mechanics during anesthesia, Engelman, E., *et al.*, (*ESA*) A.56
Equipment, tourniquets, Inhibition of increase of blood thromboxane concentration by acetylsalicylic acid after release of tourniquet in lower extremity operations, Ojanen, R., *et al.*, (*ESA*) A.94
Equipment, ventilators, Comparison of pressure support ventilation provided by two ICU ventilators, Kalfon, P., *et al.*, (*ESA*) A.182
Equipment, warming devices, An investigation into the effect of passive and active cutaneous warming devices on intraoperative body temperature in elderly patients, Bennet, J., *et al.*, (*ESA*) A.73
——, Effectiveness of core warming on net transfer of body heat across the skin, Kulkarni, P., *et al.*, (*ESA*) A.70
——, Evaluation of a forced-air warmer (Bair-Hugger) in maintaining body temperature in infants during cleft palate surgery, Murat, I., *et al.*, (*ESA*) A.166
——, Evaluation of the efficacy of forced-air warmer (Bair Hugger) during spinal surgery in children, Murat, I., *et al.*, (*ESA*) A.165
——, Preoperative skin-surface warming reduces intraoperative hypothermia, Camus, Y., *et al.*, (*ESA*) A.72
Eye, cataract, Pharmacokinetics and effects of i.m. alfentanil as premedication for outpatient cataract surgery, Ali-Melkkilä, T., *et al.*, (*ESA*) A.145
Eye, orbicularis oculi, Monitoring the onset of neuromuscular blockade at the orbicularis oculi can predict good intubating conditions when using $2 \times ED_{95}$ of atracurium, Debaene, B., *et al.*, (*ESA*) A.142

Fluid balance, Effects of desmopressin (DDAVP) supplementation in brain dead organ donors (BDOD) on early recipient renal function, Guesde, R., *et al.*, (*ESA*) A.79
Fluids, irrigating, Glycine and its metabolites during and after intrauterine YAG laser surgery, Van Boven, M. J., *et al.*, (*ESA*) A.87
Fluids, i.v., Neonatal glycemia: does the maternal i.v. fluid regimen during labor make a difference? Menigaux, C., *et al.*, (*ESA*) A.175
Forensic medicine, Midazolam premedication: a forensic approach to pharmacokinetics and amnesia, Motsch, J., *et al.*, (*ESA*) A.155
Formulations, bupivacaine, Epidural administration of liposomal bupivacaine for the management of postsurgical pain, Boogaerts, J., *et al.*, (*ESA*) A.200
Formulations, diazepam, Effects of diazepam additives on the mononuclear phagocytic system, Catalá, J. C., *et al.*, (*ESA*) A.89
Formulations, diluents, Effects of diazepam additives on the mononuclear phagocytic system, Catalá, J. C., *et al.*, (*ESA*) A.89
Formulations, etomidate, Adrenocortical function: a clinical comparison of Etomidat-Lipuro® and Hypnomidate®, Wiebalck, A., *et al.*, (*ESA*) A.90
——, Quality of Induction: a clinical comparison of Etomidat-Lipuro® and Hypnomidate®, Wiebalck, A., *et al.*, (*ESA*) A.154
Formulations, liposomes, Epidural administration of liposomal bupivacaine for the management of postsurgical pain, Boogaerts, J., *et al.*, (*ESA*) A.200
——, Motor blockade and absence of local nerve toxicity induced by liposomal bupivacaine injected into the axillary brachial plexus of rabbits, Legros, F. J., *et al.*, (*ESA*) A.122
Formulations, pH, Slow-release effect of pH-adjusted bupivacaine: pharmacokinetic demonstration, Benhamou, D., *et al.*, (*ESA*) A.120

Gastrointestinal tract, intestine, Local *versus* neurogenic vasodilator effects of desflurane and isoflurane in the small intestine, Sundeman, H., *et al.*, (*ESA*) A.50
Gastrointestinal tract, mucosal perfusion, Gastric mucosal perfusion is better preserved during cardiac surgery when isoflurane rather than enflurane or propofol is used to maintain anaesthesia, Mythen, M., *et al.*, (*ESA*) A.29
——, Influence of N-acetylcysteine on O_2 consumption and gastric intramucosal pH in septic patients, Spies, C., *et al.*, (*ESA*) A.186
——, Measurement of sigmoid intramural pH during orthotopic liver transplantation, Auroy, Y., *et al.*, (*ESA*) A.76
Genetic factors, hyperthermia, Exercise and malignant hyperthermia: family investigations, Kozak Ribbens, G., *et al.*, (*ESA*) A.92

Heart, arrhythmia, fibrillation ventricular, Pre- and intraoperative prevention by β-blockers, propranolol and esmolol, of ischaemia-induced ventricular fibrillation, Freysz, M., *et al.*, (*ESA*) A.46
Heart, blood flow, myocardial, Effects of hypertonic saline on coronary blood flow and myocardial performance of a blood-perfused, isolated rabbit heart, Delayance, S., *et al.*, (*ESA*) A.45
Heart, cardiac massage, The choice of ECM rate could improve the neuroprotection during CPR, Iannuzzi, E., *et al.*, (*ESA*) A.195
Heart, cardiac output, Alternating right to left ventricular ejection; the case of occult cardiac tamponade, Skourtis, C., *et al.*, (*ESA*) A.36
——, Cardiac output determined from pulmonary gas exchange, Österlund, B., *et al.*, (*ESA*) A.19
——, Cardiac output (CO) measurement: comparison of esophageal Doppler (ED) *vs* thermodilution (TD), Lefrant, J. Y., *et al.*, (*ESA*) A.18
——, Determinants of systolic pressure variation in patients ventilated after vascular surgery, Beaussier, M., *et al.*, (*ESA*) A.37
——, Evaluation in intensive care of the fraction area change obtained by automatic border detection, Liu, N., *et al.*, (*ESA*) A.25
——, The choice of ECM rate could improve the neuroprotection during CPR, Iannuzzi, E., *et al.*, (*ESA*) A.195
Heart, cardiopulmonary bypass, Acute preoperative plasmapheresis during cardiac surgery, Armellin, G., *et al.*, (*ESA*) A.104
——, Comparison of dobutamine with enoximone following open heart surgery in small children, Innes, P., *et al.*, (*ESA*) A.167
——, High dose aprotinin *versus* desmo-pressin acetate treatment in cardiac surgery, Hidalgo, F., *et al.*, (*ESA*) A.99
——, The relationship between cardiopulmonary bypass related immunologic effects and complement, thromboxane and leucocyte parameters, Durak, P., *et al.*, (*ESA*) A.96
Heart, catheterization, Evaluation of cardiac function in ICU: right heart catheterization *vs* transesophageal echocardiography. Preliminary results, Vivien, B., *et al.*, (*ESA*) A.183
Heart, conduction, Lemakalim reverses ventricular conduction impairment induced by a large dose of bupivacaine in anesthetized dogs, de La Coussaye, J. E., *et al.*, (*ESA*) A.121
Heart, congenital defects, Extracorporeal membrane oxygenation for postoperative cardiac support in newborn infants: first clinical data, Marcassa, A., *et al.*, (*ESA*) A.168
Heart, coronary artery bypass, Core–peripheral temperature difference in early *vs* later extubation after coronary artery surgery, Knapik, P., *et al.*, (*ESA*) A.69
——, Does routine preoperative coronary angiography modify outcome after aortic surgery? Gosgnach, M., *et al.*, (*ESA*) A.6
——, Early postperfusion assessment of gas exchange and postoperative extubation outcome following coronary artery surgery, Knapik, P., *et al.*, (*ESA*) A.61
——, Echocardiographic study of the induction with a low-dose of sufentanil for coronary artery surgery, Bromberg, N., *et al.*, (*ESA*) A.28
——, Gastric mucosal perfusion is better preserved during cardiac surgery when isoflurane rather than enflurane or propofol is used to maintain anaesthesia, Mythen, M., *et al.*, (*ESA*) A.29
——, Indications for coronary revascularisation in vascular surgical patients, Gosgnach, M., *et al.*, (*ESA*) A.5
——, Preoperative clonidine improves postoperative renal function in CABG patients, Kulka, P. J., *et al.*, (*ESA*) A.143
Heart, coronary occlusion, Effects of nitrous oxide (N_2O) on systemic haemodynamics, regional left ventricular (LV) function and incidence of myocardial ischaemia (MI) in vascular surgical patients with coronary artery disease (CAD), Hohner, P., *et al.*, (*ESA*) A.41
Heart, dobutamine, Comparison of dobutamine with

enoximone following open heart surgery in small children, Innes, P., *et al.*, (*ESA*) A.167

Heart, enoximone, Comparison of dobutamine with enoximone following open heart surgery in small children, Innes, P., *et al.*, (*ESA*) A.167

Heart, esmolol, Pre- and intraoperative prevention by β-blockers, propranolol and esmolol, of ischaemia-induced ventricular fibrillation, Freysz, M., *et al.*, (*ESA*) A.46

Heart, heart rate, Pre- and intraoperative prevention by β-blockers, propranolol and esmolol, of ischaemia-induced ventricular fibrillation, Freysz, M., *et al.*, (*ESA*) A.46

Heart, ischaemia, Dipyridamole-TEE and 24 h Holter-ECG as preoperative screening tests for coronary artery disease in patients with abdominal aortic aneurysm, Östman, M., *et al.*, (*ESA*) A.22

——, Effects of nitrous oxide (N_2O) on systemic haemodynamics, regional left ventricular (LV) function and incidence of myocardial ischaemia (MI) in vascular surgical patients with coronary artery disease (CAD), Hohner, P., *et al.*, (*ESA*) A.41

——, Epidural clonidine and myocardial ischaemia after abdominal aortic surgery, Fulgencio, J. P., *et al.*, (*ESA*) A.42

——, Evaluation of haemodynamic indices of myocardial ischaemia in patients with coronary artery disease (CAD), Hohner, P., *et al.*, (*ESA*) A.23

——, Functional recovery after 24 h preservation of rabbit hearts in University Wisconsin solution, Fellahi, J. L., *et al.*, (*ESA*) A.44

——, Influence of cervicothoracic epidural anaesthesia (C-TEA) on left ventricular (LV) contractility—an experimental study in pigs with autonomous blockade, Reiz, S., *et al.*, (*ESA*) A.52

——, Influence of positive pressure ventilation on myocardial ischaemia after abdominal aortic aneurysm repair, McCoy, D., *et al.*, (*ESA*) A.43

——, Pre- and intraoperative prevention by β-blockers, propranolol and esmolol, of ischaemia-induced ventricular fibrillation, Freysz, M., *et al.*, (*ESA*) A.46

——, Sensitivity and specificity of mechanical and electrocardiographic myocardial ischaemia (MI) monitoring techniques, Hohner, P., *et al.*, (*ESA*) A.26

——, The use of the CUSUM plot for determination of myocardial ischaemia threshold during atrial pacing in patients with coronary artery disease, Reiz, S., *et al.*, (*ESA*) A.24

——, Tolerance of preoperative transesophageal echocardiography in patients scheduled for aortic surgery, Gosgnach, M., *et al.*, (*ESA*) A.21

Heart, isolated preparation, Effects of hypertonic saline on coronary blood flow and myocardial performance of a blood-perfused, isolated rabbit heart, Delayance, S., *et al.*, (*ESA*) A.45

——, Functional recovery after 24 h preservation of rabbit hearts in University Wisconsin solution, Fellahi, J. L., *et al.*, (*ESA*) A.44

Heart, isoprenaline, Pulmonary and systemic vascular effects of isoproterenol, nitroglycerin and prostaglandin E1 early after cardiac operations in patients with pulmonary hypertension, Alvarez, J., *et al.*, (*ESA*) A.27

Heart, myocardial function, Cardiac function in aneurysmal subarachnoid haemorrhage, Moulay, N., *et al.*, (*ESA*) A.108

——, Effects of hypertonic saline on coronary blood flow and myocardial performance of a blood-perfused, isolated rabbit heart, Delayance, S., *et al.*, (*ESA*) A.45

——, Evaluation of cardiac function in ICU: right heart catheterization *vs* transesophageal echocardiography. Preliminary results, Vivien, B., *et al.*, (*ESA*) A.183

——, Evaluation of haemodynamic indices of myocardial ischaemia in patients with coronary artery disease (CAD), Hohner, P., *et al.*, (*ESA*) A.23

——, Functional recovery after 24 h preservation of rabbit hearts in University Wisconsin solution, Fellahi, J. L., *et al.*, (*ESA*) A.44

——, Propofol/fentanyl-anesthesia in patients with highly depressed cardiac function, Rauch, H., *et al.*, (*ESA*) A.30

——, Tolerance of preoperative transesophageal echocardiography in patients scheduled for aortic surgery, Gosgnach, M., *et al.*, (*ESA*) A.21

Heart, nitroglycerin, Pulmonary and systemic vascular effects of isoproterenol, nitroglycerin and prostaglandin E1 early after cardiac operations in patients with pulmonary hypertension, Alvarez, J., *et al.*, (*ESA*) A.27

Heart, pacemakers artificial, EEG-monitoring during defibrillator-implantation: effects of repetitive cerebral ischemia on electric brain activity, Spies, C., *et al.*, (*ESA*) A.110

Heart, preservation, Functional recovery after 24 h preservation of rabbit hearts in University Wisconsin solution, Fellahi, J. L., *et al.*, (*ESA*) A.44

Heart, propranolol, Pre- and intraoperative prevention by β-blockers, propranolol and esmolol, of ischaemia-induced ventricular fibrillation, Freysz, M., *et al.*, (*ESA*) A.46

Heart, resuscitation, The choice of ECM rate could improve the neuroprotection during CPR, Iannuzzi, E., *et al.*, (*ESA*) A.195

Heart, tamponade, Alternating right to left ventricular ejection; the case of occult cardiac tamponade, Skourtis, C., *et al.*, (*ESA*) A.36

Heart, transplantation, Functional recovery after 24 h preservation of rabbit hearts in University Wisconsin solution, Fellahi, J. L., *et al.*, (*ESA*) A.44

Heart, vascular pressures, A comparison between various hemodynamic parameters reflecting preload during traded hemorrhage in ventilated dogs, Preisman, S., *et al.*, (*ESA*) A.51

——, Alternating right to left ventricular ejection; the case of occult cardiac tamponade, Skourtis, C., *et al.*, (*ESA*) A.36

——, Determinants of systolic pressure variation in patients ventilated after vascular surgery, Beaussier, M., *et al.*, (*ESA*) A.37

——, Evaluation of haemodynamic indices of myocardial ischaemia in patients with coronary artery disease (CAD), Hohner, P., *et al.*, (*ESA*) A.23

——, Influence of chronic angiotensin converting enzyme inhibition on systolic pressure variation during anesthetic induction, Puybasset, L., *et al.*, (*ESA*) A.39

——, The systolic pressure variation predicts response to volume loading in patients ventilated after aortic surgery, Coriat, P., *et al.*, (*ESA*) A.38

Heart, ventricles, Effects of nitrous oxide (N_2O) on systemic haemodynamics, regional left ventricular (LV) function and incidence of myocardial ischaemia (MI) in vascular surgical patients with coronary artery disease (CAD), Hohner, P., *et al.*, (*ESA*) A.41

——, Effects of plasma volume substitution on right ventricle volumes and function using Elohes® and Plasmion®, Lepage, J. Y., *et al.*, (*ESA*) A.35

——, Endocardial endothelium modulates *in vivo* left ventricular performance, De Hert, S. G., *et al.*, (*ESA*) A.47

——, Influence of cervicothoracic epidural anaesthesia (C-TEA) on left ventricular (LV) contractility—an experimental study in pigs with autonomous blockade, Reiz, S., *et al.*, (*ESA*) A.52

——, Influence of chronic angiotensin converting enzyme inhibition on systolic pressure variation during anesthetic induction, Puybasset, L., *et al.*, (*ESA*) A.39

——, The systolic pressure variation predicts response to volume loading in patients ventilated after aortic surgery, Coriat, P., *et al.*, (*ESA*) A.38

Histamine, antihistamines, The combined prophylactic administration of H1 and H2 receptor blockers in the prevention of protamine related haemodynamic effects and the relation between antihistaminics-leucocytes and pulmonary vascular resistance, Durak, P., *et al.*, (*ESA*) A.95

Hormones, adrenal, Adrenocortical function: a clinical comparison of Etomidat-Lipuro® and Hypnomidate®, Wiebalck, A., *et al.*, (*ESA*) A.90

Hormones, adrenocorticotrophic, Adrenocortical function: a clinical comparison of Etomidat-Lipuro® and Hypnomidate®, Wiebalck, A., *et al.*, (*ESA*) A.90

Hormones, aldosterone, Modification of the renin–aldosterone axis during orthotopic liver transplantation, De los Ríos, J., *et al.*, (*ESA*) A.75

Hormones, antidiuretic, Effects of desmopressin (DDAVP) supplementation in brain dead organ donors (BDOD) on early recipient renal function, Guesde, R., *et al.*, (*ESA*) A.79

——, High dose aprotinin *versus* desmo-pressin acetate treatment in cardiac surgery, Hidalgo, F., *et al.*, (*ESA*) A.99

Hormones, corticosteroid, Diaphragmatic function after bupivacaine cervical extradural analgesia for chronic pain therapy, Nyström, E., *et al.*, (*ESA*) A.65

Hormones, growth, Effect of recombinant human growth hormone (HGH) on protein metabolism in surgical patients, Carli, F., *et al.*, (*ESA*) A.86

Hormones, insulin, Isoflurane inhibits Ca^{2+}-induced insulin secretion from electrically permeabilised islets of Langerhans, Desborough, J. P., *et al.*, (*ESA*) A.91

Hormones, progesterone, Adrenocortical function: a clinical comparison of Etomidat-Lipuro® and Hypnomidate®, Wiebalck, A., *et al.*, (*ESA*) A.90

Hormones, prostaglandins, Pulmonary and systemic vascular effects of isoproterenol, nitroglycerin and prostaglandin E1 early after cardiac operations in patients with pulmonary hypertension, Alvarez, J., *et al.*, (*ESA*) A.27

Hormones, renin, Adrenocortical function: a clinical comparison of Etomidat-Lipuro® and Hypnomidate®, Wiebalck, A., *et al.*, (*ESA*) A.90

——, Modification of the renin–aldosterone axis during orthotopic liver transplantation, De los Ríos, J., *et al.*, (*ESA*) A.75

Hypnotics benzodiazepine, diazepam, Effects of diazepam additives on the mononuclear phagocytic system, Catalá, J. C., *et al.*, (*ESA*) A.89

Hypnotics benzodiazepine, midazolam, A comparison of midazolam and midazolam plus fentanyl for colonoscopy, Dupont, H., *et al.*, (*ESA*) A.9

——, Dexmedetomidine does not exercise its anesthetic action through GABA, Salonen, M., *et al.*, (*ESA*) A.113

——, Dose dependent effects of oral medication with midazolam, Biro, P., *et al.*, (*ESA*) A.156

——, Midazolam premedication: a forensic approach to pharmacokinetics and amnesia, Motsch, J., *et al.*, (*ESA*) A.155

——, Midazolam prevents ketamine-induced stimulation of cerebral metabolism, Åkeson, J., *et al.*, (*ESA*) A.111

——, Prolonged (> 1 week) sedation with midazolam in ICU patients: efficacy, safety and pharmacokinetics, Heytens, L., *et al.*, (*ESA*) A.178

Hypoxaemia, Continuous monitoring of Sp_{O_2} during total intravenous anaesthesia with ketamine and spontaneous ventilation, Joly, L.-M., *et al.*, (*ESA*) A.58

——, Hypoxic events after general anaesthesia in the recovery room, Degasperi, D., *et al.*, (*ESA*) A.59

——, Influence of anaesthesia on post-operative hypoxaemia, Georgiou, L., *et al.*, (*ESA*) A.60

——, Postoperative hypoxaemia: comparison of epidural and patient controlled analgesia, Spencer, A., *et al.*, (*ESA*) A.207

Immune response, The relationship between cardiopulmonary bypass related immunologic effects and complement, thromboxane and leucocyte parameters, Durak, P., *et al.*, (*ESA*) A.96

Immune response, suppression, Effects of diazepam additives on the mononuclear phagocytic system, Catalá, J. C., *et al.*, (*ESA*) A.89

——, Is the vasoconstrictive effect of cyclosporine mediated by endothelin in kidney transplantation? Mouquet, C., *et al.*, (*ESA*) A.84

Induction, anaesthesia, Echocardiographic study of the induction with a low-dose of sufentanil for coronary artery surgery, Bromberg, N., *et al.*, (*ESA*) A.28

——, Influence of chronic angiotensin converting enzyme inhibition on systolic pressure variation during anesthetic induction, Puybasset, L., *et al.*, (*ESA*) A.39

——, Ketamine does not prevent hypotension caused by induction of anaesthesia with propofol in elderly patients, Blockmans, D., *et al.*, (*ESA*) A.40

Infants, Comparison of dobutamine with enoximone following open heart surgery in small children, Innes, P., *et al.*, (*ESA*) A.167

——, Evaluation of a forced-air warmer (Bair-Hugger) in maintaining body temperature in infants during cleft palate surgery, Murat, I., *et al.*, (*ESA*) A.166

——, The pharmacokinetics of rocuronium in pediatric patients: a pooled data analysis, Meistelman, C., *et al.*, (*ESA*) A.138

——, Use of thoracic epidural block for perioperative analgesia in children, Entress, A. H., *et al.*, (*ESA*) A.158

——, Ventilation with halothane is less affected in children with laryngeal mask airway than with endotracheal tube, Reignier, J., *et al.*, (*ESA*) A.162

Infection, bacterial, Incidence of bacterial maxillary sinusitis in critically ill patients with radiologic maxillary sinusitis, Bodin, L., *et al.*, (*ESA*) A.179

——, Molecular mediators and cardiac surgery, Pérez Arancón, J. L., *et al.*, (*ESA*) A.188

——, Molecular mediators and post-bacteraemic phase, Martínez Urionabarrenetxea, K., *et al.*, (*ESA*) A.187

Infection, central nervous system, External ventricular CSF drains infections, Mahé, V., *et al.*, (*ESA*) A.109

Infection, nosocomial, External ventricular CSF drains infections, Mahé, V., *et al.*, (*ESA*) A.109

——, Incidence of bacterial maxillary sinusitis in critically ill patients with radiologic maxillary sinusitis, Bodin, L., *et al.*, (*ESA*) A.179

Intensive care, Cardiac output(CO) measurement: comparison of esophageal Doppler (ED) *vs* thermodilution (TD), Lefrant, J. Y., *et al.*, (*ESA*) A.18

——, Comparison of pressure support ventilation provided by two ICU ventilators, Kalfon, P., *et al.*, (*ESA*) A.182

——, Comparison of two therapeutic strategies of septic shock, Martin, C., *et al.*, (*ESA*) A.190

——, Continuous monitoring of the ventilatory mechanics during anaesthesia & intensive care, Py, C., *et al.*, (*ESA*) A.57

——, Evaluation in intensive care of the fraction area change obtained by automatic border detection, Liu, N., *et al.*, (*ESA*) A.25

——, Evaluation of cardiac function in ICU: right heart catheterization *vs* transesophageal echocardiography. Preliminary results, Vivien, B., *et al.*, (*ESA*) A.183

——, Histology aspects of pulmonary barotrauma in critically ill patients with acute respiratory failure, Rouby, J. J., *et al.*, (*ESA*) A.181

——, Influence of N-acetylcysteine on O_2 consumption and gastric intramucosal pH in septic patients, Spies, C., *et al.*, (*ESA*) A.186

——, Molecular mediators and cardiac surgery, Pérez Arancón, J. L., *et al.*, (*ESA*) A.188

——, Non invasive monitoring of CO_2 in patients with septic shock, Bodin, L., *et al.*, (*ESA*) A.191

——, Outcome for patients in intensive care with acute renal failure requiring dialysis, Ejlersen, E., *et al.*, (*ESA*) A.7

——, Preservation of humidity and heat of respiratory gases in patients with minute ventilation > 10 l/min, Martin, C., *et al.*, (*ESA*) A.20

——, Septic shock: effect of a goal-directed therapy on oxygen metabolism and serum cytokine levels, Martin, C., *et al.*, (*ESA*) A.189

——, Technical aspects of jugular bulb oximetry, De Deyne, C., *et al.*, (*ESA*) A.16

Intensive care, alcohol withdrawal, Carbohydrate deficient transferrin: a new copredictor of alcoholism related postoperative complications? Heil, T., *et al.*, (*ESA*) A.88

Intensive care, audit, A national database for intensive care medicine in Sweden, Karling, M., (*ESA*) A.8

Intensive care, infections, Incidence of bacterial maxillary sinusitis in critically ill patients with radiologic maxillary sinusitis, Bodin, L., *et al.*, (*ESA*) A.179

——, Molecular mediators and post-bacteraemic phase, Martínez Urionabarrenetxea, K., *et al.*, (*ESA*) A.187

Intensive care, sedation, Prolonged (> 1 week) sedation with midazolam in ICU patients: efficacy, safety and pharmacokinetics, Heytens, L., *et al.*, (*ESA*) A.178

Interactions (drug), Does nicardipine potentiate the neuromuscular block of atracurium? Bazin, J. E., *et al.*, (*ESA*) A.136

——, Isoproterenol reverses the MAC decreasing effect of esmolol in rats, Perel, A., *et al.*, (*ESA*) A.117

——, Midazolam prevents ketamine-induced stimulation of cerebral metabolism, Åkeson, J., *et al.*, (*ESA*) A.111

——, The effect of parenteral diclofenac and morphine on efficacy duration and height of blockade during continuous epidural bupivacaine 0.5%, Forbes, D., *et al.*, (*ESA*) A.125

Intubation tracheal, Monitoring the onset of neuromuscular blockade at the orbicularis oculi can predict good intubating conditions when using $2 \times ED_{95}$ of atracurium, Debaene, B., *et al.*, (*ESA*) A.142

——, Propofol for tracheal intubation in paediatric outpatient anaesthesia, Montasser, A. M., (*ESA*) A.161

Intubation tracheal, difficult, A new clinical score to predict difficult intubation, Arné, J., *et al.*, (*ESA*) A.1

Intubation tracheal, extubation, Core–peripheral temperature difference in early *vs* later extubation after coronary artery surgery, Knapik, P., *et al.*, (*ESA*) A.69

——, Early postperfusion assessment of gas exchange and postoperative extubation outcome following coronary artery surgery, Knapik, P., *et al.*, (*ESA*) A.61

Intubation tracheal, responses, Effect of esmolol *versus* lidocaine on intracranial pressure and haemodynamic responses to laryngoscopy and intubation, Samaha, T., *et al.*, (*ESA*) A.118

Ions, calcium, Isoflurane inhibits Ca^{2+}-induced insulin secretion from electrically permeabilised islets of Langerhans, Desborough, J. P., *et al.*, (*ESA*) A.91

Ions, magnesium, Priming of atracurium with magnesium, Lampl, E., *et al.*, (*ESA*) A.139

Ions, sodium, Effects of hypertonic saline on coronary blood flow and myocardial performance of a blood-perfused, isolated rabbit heart, Delayance, S., *et al.*, (*ESA*) A.45

——, Modification of the renin–aldosterone axis during orthotopic liver transplantation, De los Ríos, J., *et al.*, (*ESA*) A.75

Kidney, blood flow, Renal blood flow and function relationship in recent renal transplantation in man, Jacob, L., *et al.*, (*ESA*) A.85

Kidney, failure, Is the vasoconstrictive effect of cyclosporine mediated by endothelin in kidney transplantation? Mouquet, C., *et al.*, (*ESA*) A.84
——, Outcome for patients in intensive care with acute renal failure requiring dialysis, Ejlersen, E., *et al.*, (*ESA*) A.7
——, Pharmacokinetics of propofol and its conjugates after continuous infusion in normal and renal failure patients, Nathan, N., *et al.*, (*ESA*) A.151
——, Prevention of acute tubular necrosis by volume loading in kidney transplantation, Mouquet, C., *et al.*, (*ESA*) A.82
——, Volume loading and hormonal factors in the prevention of acute tubular necrosis in kidney transplantation, Mouquet, C., *et al.*, (*ESA*) A.83
Kidney, function, Effects of desmopressin (DDAVP) supplementation in brain dead organ donors (BDOD) on early recipient renal function, Guesde, R., *et al.*, (*ESA*) A.79
——, Preoperative clonidine improves postoperative renal function in CABG patients, Kulka, P. J., *et al.*, (*ESA*) A.143
——, Renal blood flow and function relationship in recent renal transplantation in man, Jacob, L., *et al.*, (*ESA*) A.85
Kidney, lithotripsy, Propofol anaesthesia with spontaneous breathing for extracorporeal shock wave lithotripsy, Pasch, T., *et al.*, (*ESA*) A.153
Kidney, transplantation, Effects of desmopressin (DDAVP) supplementation in brain dead organ donors (BDOD) on early recipient renal function, Guesde, R., *et al.*, (*ESA*) A.79
——, Is the vasoconstrictive effect of cyclosporine mediated by endothelin in kidney transplantation? Mouquet, C., *et al.*, (*ESA*) A.84
——, Prevention of acute tubular necrosis by volume loading in kidney transplantation, Mouquet, C., *et al.*, (*ESA*) A.82
——, Renal blood flow and function relationship in recent renal transplantation in man, Jacob, L., *et al.*, (*ESA*) A.85
——, Total intravenous anaesthesia (TIVA) with propofol and alfentanil for renal transplantation, Kirvelä, M., *et al.*, (*ESA*) A.81
——, Volume loading and hormonal factors in the prevention of acute tubular necrosis in kidney transplantation, Mouquet, C., *et al.*, (*ESA*) A.83
Kidney, urine metabolites, Modification of the renin–aldosterone axis during orthotopic liver transplantation, De los Ríos, J., *et al.*, (*ESA*) A.75

Larynx, damage, Day 0 or day 3 laryngoscopy after thyroidectomy? Lacoste, L., *et al.*, (*ESA*) A.67
——, Direct, indirect or flexible laryngoscopy after thyroidectomy? Lacoste, L., *et al.*, (*ESA*) A.66
Larynx, laryngoscopy, Day 0 or day 3 laryngoscopy after thyroidectomy? Lacoste, L., *et al.*, (*ESA*) A.67
——, Direct, indirect or flexible laryngoscopy after thyroidectomy? Lacoste, L., *et al.*, (*ESA*) A.66
——, Effect of esmolol ***versus*** lidocaine on intracranial pressure and haemodynamic responses to laryngoscopy and intubation, Samaha, T., *et al.*, (*ESA*) A.118
——, Laryngeal function as assessed by tussometry following topical anaesthesia, Mahajan, R. P., *et al.*, (*ESA*) A.68
Larynx, laryngoscopy fibreoptic, Direct, indirect or flexible laryngoscopy after thyroidectomy? Lacoste, L., *et al.*, (*ESA*) A.66
Larynx, vocal cords, Concentration–effect relationship at the vocal cords and the adductor pollicis following rocuronium administration, Plaud, B., *et al.*, (*ESA*) A.141
——, Laryngeal function as assessed by tussometry following topical anaesthesia, Mahajan, R. P., *et al.*, (*ESA*) A.68
Liver, blood flow, The effect of dobutamine and norepinephrine on global and splanchnic O_2 consumption, Meier-Hellmann, A., *et al.*, (*ESA*) A.185
Liver, cirrhosis, Modification of the renin–aldosterone axis during orthotopic liver transplantation, De los Ríos, J., *et al.*, (*ESA*) A.75
——, Oxygen consumption is dependent upon oxygen delivery in cirrhotics undergoing liver transplantation, Piccinni, P., *et al.*, (*ESA*) A.78
Liver, metabolism, Influence of norepinephrine therapy on the oxygen supply and lactate extraction rate of the liver in the septic pig, Schäfer, R., *et al.*, (*ESA*) A.184
Liver, oxygen consumption, The effect of dobutamine and norepinephrine on global and splanchnic O_2 consumption, Meier-Hellmann, A., *et al.*, (*ESA*) A.185
Liver, transplantation, Blood requirements reduction in orthotopic liver transplantation with aprotinin, Monedero, P., *et al.*, (*ESA*) A.98
——, Changes in blood lactate, total body oxygen delivery and consumption during liver transplantation, Carrera, J., *et al.*, (*ESA*) A.77
——, Measurement of sigmoid intramural pH during orthotopic liver transplantation, Auroy, Y., *et al.*, (*ESA*) A.76
——, Modification of the renin–aldosterone axis during orthotopic liver transplantation, De los Ríos, J., *et al.*, (*ESA*) A.75
——, Oxygen consumption is dependent upon oxygen delivery in cirrhotics undergoing liver transplantation, Piccinni, P., *et al.*, (*ESA*) A.78
Lung, atelectasis, Recruitment of atelectasis during general anaesthesia: a CT-study, Rothen, H. U., *et al.*, (*ESA*) A.53
Lung, compliance, Influence of posture on the respiratory mechanics during anesthesia, Engelman, E., *et al.*, (*ESA*) A.56
——, The respiratory compliance in normal and obese subjects during anaesthesia, Mulazzi, D., *et al.*, (*ESA*) A.54
Lung, damage, Histology aspects of pulmonary barotrauma in critically ill patients with acute respiratory failure, Rouby, J. J., *et al.*, (*ESA*) A.181
——, Systemic gas embolism in pulmonary contusion diagnosed by transesophageal echocardiography, Saada, M., *et al.*, (*ESA*) A.194
Lung, function, Fiberoptic bronchoscopy in brain dead organ donors, Riou, B., *et al.*, (*ESA*) A.80
Lung, gas exchange, Cardiac output determined from pulmonary gas exchange, Österlund, B., *et al.*, (*ESA*) A.19
Lung, intravascular pressures, Pulmonary and systemic vascular effects of isoproterenol, nitroglycerin and prostaglandin E1 early after cardiac operations in patients with pulmonary hypertension, Alvarez, J., *et al.*, (*ESA*) A.27
Lung, lavage, Reassessment of bronchoalveolar lavage in the diagnosis of post traumatic pulmonary fat embolism, Mimoz, O., *et al.*, (*ESA*) A.180
Lung, transplantation, Fiberoptic bronchoscopy in brain dead organ donors, Riou, B., *et al.*, (*ESA*) A.80

Malignant hyperthermia, Exercise and malignant hyperthermia: family investigations, Kozak Ribbens, G., *et al.*, (*ESA*) A.92
——, Is Burkitt's lymphoma an etiology or a differential diagnosis of malignant hyperthermia? Lienhart, A., *et al.*, (*ESA*) A.93
Measurement techniques, arterial pressure, Clinical evaluation of the calibration of noninvasive continuous blood pressure measurement devices by means of oscillometric blood pressure measurements, de Jong, J. R., *et al.*, (*ESA*) A.15
Measurement techniques, carbon dioxide, Non invasive monitoring of CO_2 in patients with septic shock, Bodin, L., *et al.*, (*ESA*) A.191
Measurement techniques, cardiac output, Cardiac output determined from pulmonary gas exchange, Österlund, B., *et al.*, (*ESA*) A.19
——, Cardiac output(CO) measurement: comparison of esophageal Doppler (ED) *vs* thermodilution (TD), Lefrant, J. Y., *et al.*, (*ESA*) A.18
Measurement techniques, Doppler echocardiography, Cardiac output (CO) measurement: comparison of esophageal Doppler (ED) *vs* thermodilution (TD), Lefrant, J. Y., *et al.*, (*ESA*) A.18
Measurement techniques, neuromuscular block, Comparison between double-burst stimulation and 50, 100 Hz tetanic fade during spontaneous recovery of vecuronium induced neuromuscular blockade, Baurain, M. J., *et al.*, (*ESA*) A.133
Measurement techniques, oximeters, Technical aspects of jugular bulb oximetry, De Deyne, C., *et al.*, (*ESA*) A.16
Measurement techniques, plethysmography, The effects of epidural and spinal anesthesia on the changes in the plethysmographic signal in the lower and upper limbs, Preisman, S., *et al.*, (*ESA*) A.124
Measurement techniques, spectral analysis, Accuracy of processed auditory evoked response in predicting movement during cardiac surgery, Kuppe, H., *et al.*, (*ESA*) A.31
Measurement techniques, thermodilution, Cardiac output determined from pulmonary gas exchange, Österlund, B., *et al.*, (*ESA*) A.19
——, Cardiac output (CO) measurement: comparison of esophageal Doppler (ED) *vs* thermodilution (TD), Lefrant, J. Y., *et al.*, (*ESA*) A.18
Measurement techniques, tussometry, Laryngeal function as assessed by tussometry following topical anaesthesia, Mahajan, R. P., *et al.*, (*ESA*) A.68

Measurement techniques, ultrasound, Cerebral blood flow velocities (CBFV) during anaesthesia for gynaecological laparoscopic surgery, Granry, J. C., *et al.*, (*ESA*) A.32
——, Renal blood flow and function relationship in recent renal transplantation in man, Jacob, L., *et al.*, (*ESA*) A.85
——, Transcranial Doppler sonography: effect of propofol and thiopental in patients with brain tumors and brain injuries, Schregel, W., *et al.*, (*ESA*) A.105
Membrane, nerve, Nitrous oxide induced neuronal depression: modification through benzodiazepine receptors, Dzoljic, M., *et al.*, (*ESA*) A.112
Memory, Flumazenil facilitates intraoperative arousal in scoliosis surgery, Koscielniak-Nielsen, Z. J., *et al.*, (*ESA*) A.157
——, Midazolam premedication: a forensic approach to pharmacokinetics and amnesia, Motsch, J., *et al.*, (*ESA*) A.155
Metabolism, free radicals, Propofol (2,6 diisopropylphenol) as an antioxidant *in-vitro*: a dose response study, Bennett, S., *et al.*, (*ESA*) A.152
Metabolism, glucose, Isoflurane inhibits Ca^{2+}-induced insulin secretion from electrically permeabilised islets of Langerhans, Desborough, J. P., *et al.*, (*ESA*) A.91
——, Neonatal glycemia: does the maternal i.v. fluid regimen during labor make a difference? Menigaux, C., *et al.*, (*ESA*) A.175
Metabolism, glycine, Glycine and its metabolites during and after intrauterine YAG laser surgery, Van Boven, M. J., *et al.*, (*ESA*) A.87
Metabolism, lactate, Changes in blood lactate, total body oxygen delivery and consumption during liver transplantation, Carrera, J., *et al.*, (*ESA*) A.77
——, Influence of norepinephrine therapy on the oxygen supply and lactate extraction rate of the liver in the septic pig, Schäfer, R., *et al.*, (*ESA*) A.184
——, Jugular bulb metabolic monitoring during hyperventilation in severe head trauma patients, De Deyne, C., *et al.*, (*ESA*) A.106
——, Sensitivity and specificity of mechanical and electrocardiographic myocardial ischaemia (MI) monitoring techniques, Hohner, P., *et al.*, (*ESA*) A.26
——, The use of the CUSUM plot for determination of myocardial ischaemia threshold during atrial pacing in patients with coronary artery disease, Reiz, S., *et al.*, (*ESA*) A.24
Metabolism, midazolam, Midazolam premedication: a forensic approach to pharmacokinetics and amnesia, Motsch, J., *et al.*, (*ESA*) A.155
Metabolism, oxygen consumption, Influence of norepinephrine therapy on the oxygen supply and lactate extraction rate of the liver in the septic pig, Schäfer, R., *et al.*, (*ESA*) A.184
Metabolism, protein, Effect of recombinant human growth hormone (HGH) on protein metabolism in surgical patients, Carli, F., *et al.*, (*ESA*) A.86
Microcirculation, Influence of N-acetylcysteine on O_2 consumption and gastric intramucosal pH in septic patients, Spies, C., *et al.*, (*ESA*) A.186
Model, acute pain service, Organization of acute pain services—a low-cost model, Rawal, N., (*ESA*) A.199
Model, computer simulation, Computer-controlled syringe pump improves safety of pharmacokinetic models, Duranteau, R., *et al.*, (*ESA*) A.148
Model, mathematical, Evaluation in intensive care of the fraction area change obtained by automatic border detection, Liu, N., *et al.*, (*ESA*) A.25
——, The use of the CUSUM plot for determination of myocardial ischaemia threshold during atrial pacing in patients with coronary artery disease, Reiz, S., *et al.*, (*ESA*) A.24
Model, pharmacokinetic, Computer-controlled syringe pump improves safety of pharmacokinetic models, Duranteau, R., *et al.*, (*ESA*) A.148
——, Determination of a pharmacokinetic model for propofol induction of anaesthesia, Viviand, X., *et al.*, (*ESA*) A.150
Monitoring, angiography, Dipyridamole-TEE and 24 h Holter-ECG as preoperative screening tests for coronary artery disease in patients with abdominal aortic aneurysm, Östman, M., *et al.*, (*ESA*) A.22
——, Does routine preoperative coronary angiography modify outcome after aortic surgery? Gosgnach, M., *et al.*, (*ESA*) A.6
——, Indications for coronary revascularisation in vascular surgical patients, Gosgnach, M., *et al.*, (*ESA*) A.5
Monitoring, carbon dioxide, Non invasive monitoring of CO_2 in patients with septic shock, Bodin, L., *et al.*, (*ESA*) A.191
Monitoring, computerized, Continuous monitoring of the ventilatory mechanics during anaesthesia & intensive care, Py, C., *et al.*, (*ESA*) A.57
——, Evaluation in intensive care of the fraction area change obtained by automatic border detection, Liu, N., *et al.*, (*ESA*) A.25
——, Sensitivity and specificity of mechanical and electrocardiographic myocardial ischaemia (MI) monitoring techniques, Hohner, P., *et al.*, (*ESA*) A.26
——, The use of the CUSUM plot for determination of myocardial ischaemia threshold during atrial pacing in patients with coronary artery disease, Reiz, S., *et al.*, (*ESA*) A.24
Monitoring, depth of anaesthesia, Accuracy of processed auditory evoked response in predicting movement during cardiac surgery, Kuppe, H., *et al.*, (*ESA*) A.31
Monitoring, echocardiography, Cardiac function in aneurysmal subarachnoid haemorrhage, Moulay, N., *et al.*, (*ESA*) A.108
——, Determinants of systolic pressure variation in patients ventilated after vascular surgery, Beaussier, M., *et al.*, (*ESA*) A.37
——, Diagnosis of aortic rupture by transesophageal echocardiography (TEE), Goarin, J. P., *et al.*, (*ESA*) A.193
——, Dipyridamole-TEE and 24 h Holter-ECG as preoperative screening tests for coronary artery disease in patients with abdominal aortic aneurysm, Östman, M., *et al.*, (*ESA*) A.22
——, Echocardiographic study of the induction with a low-dose of sufentanil for coronary artery surgery, Bromberg, N., *et al.*, (*ESA*) A.28
——, Evaluation in intensive care of the fraction area change obtained by automatic border detection, Liu, N., *et al.*, (*ESA*) A.25
——, Evaluation of cardiac function in ICU: right heart catheterization *vs* transesophageal echocardiography. Preliminary results, Vivien, B., *et al.*, (*ESA*) A.183
——, Evaluation of systematic TEE in patients suspected of blunt chest trauma, Catoire, P., *et al.*, (*ESA*) A.192
——, Sensitivity and specificity of mechanical and electrocardiographic myocardial ischaemia (MI) monitoring techniques, Hohner, P., *et al.*, (*ESA*) A.26
——, Systemic gas embolism in pulmonary contusion diagnosed by transesophageal echocardiography, Saada, M., *et al.*, (*ESA*) A.194
——, Tolerance of preoperative transesophageal echocardiography in patients scheduled for aortic surgery, Gosgnach, M., *et al.*, (*ESA*) A.21
Monitoring, electrocardiography, Cardiac function in aneurysmal subarachnoid haemorrhage, Moulay, N., *et al.*, (*ESA*) A.108
——, Dipyridamole-TEE and 24 h Holter-ECG as preoperative screening tests for coronary artery disease in patients with abdominal aortic aneurysm, Östman, M., *et al.*, (*ESA*) A.22
——, Mechanisms of ECG changes during caesarean section (CS)—a hypothesis, Svanström, M., *et al.*, (*ESA*) A.177
——, Sensitivity and specificity of mechanical and electrocardiographic myocardial ischaemia (MI) monitoring techniques, Hohner, P., *et al.*, (*ESA*) A.26
Monitoring, electroencephalography, EEG-monitoring during defibrillator-implantation: effects of repetitive cerebral ischemia on electric brain activity, Spies, C., *et al.*, (*ESA*) A.110
Monitoring, electro-oculogram, Evaluation of saccadic eye movements as an objective test during recovery from anesthesia, Paut, O., *et al.*, (*ESA*) A.10
Monitoring, evoked potentials, Accuracy of processed auditory evoked response in predicting movement during cardiac surgery, Kuppe, H., *et al.*, (*ESA*) A.31
Monitoring, oxygen, Continuous monitoring of Sp_{O_2} during total intravenous anaesthesia with ketamine and spontaneous ventilation, Joly, L.-M., *et al.*, (*ESA*) A.58
——, Hypoxic events after general anaesthesia in the recovery room, Degasperi, D., *et al.*, (*ESA*) A.59
——, Technical aspects of jugular bulb oximetry, De Deyne, C., *et al.*, (*ESA*) A.16
Monitoring, spirometry, Continuous spirometry: an aid in the intraoperative respiratory monitoring—case reports, Bardoczky, G., *et al.*, (*ESA*) A.55
Monitoring, sympathetic block, The effects of epidural and spinal anesthesia on the changes in the plethysmographic signal in the lower and upper limbs, Preisman, S., *et al.*, (*ESA*) A.124
Monitoring, vectorcardiography, Sensitivity and specificity of mechanical and electrocardiographic myocardial ischaemia (MI) monitoring techniques, Hohner, P., *et al.*, (*ESA*) A.26
——, The use of the CUSUM plot for determination of

myocardial ischaemia threshold during atrial pacing in patients with coronary artery disease, Reiz, S., *et al.*, (*ESA*) A.24
Monitoring, ventilation, Continuous monitoring of the ventilatory mechanics during anaesthesia & intensive care, Py, C., *et al.*, (*ESA*) A.57
Muscle cardiac, contractility, Endocardial endothelium modulates *in vivo* left ventricular performance, De Hert, S. G., *et al.*, (*ESA*) A.47
——, Influence of cervicothoracic epidural anaesthesia (C-TEA) on left ventricular (LV) contractility—an experimental study in pigs with autonomous blockade, Reiz, S., *et al.*, (*ESA*) A.52
Muscle skeletal, diaphragm, Diaphragmatic function after bupivacaine cervical extradural analgesia for chronic pain therapy, Nyström, E., *et al.*, (*ESA*) A.65

Neonates, Extracorporeal membrane oxygenation for postoperative cardiac support in newborn infants: first clinical data, Marcassa, A., *et al.*, (*ESA*) A.168
——, Neonatal glycemia: does the maternal i.v. fluid regimen during labor make a difference? Menigaux, C., *et al.*, (*ESA*) A.175
Nerve, membrane, Nitrous oxide induced neuronal depression: modification through benzodiazepine receptors, Dzoljic, M., *et al.*, (*ESA*) A.112
Neuromuscular block, antagonism, Reversal of vecuronium induced neuromuscular blockade: No effects of atropine administration timing, Baurain, M. J., *et al.*, (*ESA*) A.134
Neuromuscular block, atracurium, Does nicardipine potentiate the neuromuscular block of atracurium? Bazin, J. E., *et al.*, (*ESA*) A.136
——, Monitoring the onset of neuromuscular blockade at the orbicularis oculi can predict good intubating conditions when using $2 \times ED_{95}$ of atracurium, Debaene, B., *et al.*, (*ESA*) A.142
——, Neostigmine antagonism of neuromuscular blockade induced by mivacurium, vecuronium and atracurium, Dernovoi, B. S., *et al.*, (*ESA*) A.137
——, Priming of atracurium with magnesium, Lampl, E., *et al.*, (*ESA*) A.139
——, Supra-additivity between atracurium and vecuronium, Meretoja, O. A., *et al.*, (*ESA*) A.140
Neuromuscular block, measurement of response, Can repetition of high frequencies stimuli alter the value of 50 and 100 Hz tetanic fade during vecuronium induced neuromuscular blockade? Baurain, M. J., *et al.*, (*ESA*) A.135
——, Comparison between double-burst stimulation and 50, 100 Hz tetanic fade during spontaneous recovery of vecuronium induced neuromuscular blockade, Baurain, M. J., *et al.*, (*ESA*) A.133
——, Monitoring the onset of neuromuscular blockade at the orbicularis oculi can predict good intubating conditions when using $2 \times ED_{95}$ of atracurium, Debaene, B., *et al.*, (*ESA*) A.142
Neuromuscular block, mivacurium, Neostigmine antagonism of neuromuscular blockade induced by mivacurium, vecuronium and atracurium, Dernovoi, B. S., *et al.*, (*ESA*) A.137
——, Neuromuscular blockade following mivacurium in children during N_2O–halothane, Orliaguet, G., *et al.*, (*ESA*) A.163
Neuromuscular block, potentiation, Does nicardipine potentiate the neuromuscular block of atracurium? Bazin, J. E., *et al.*, (*ESA*) A.136
Neuromuscular block, priming, Priming of atracurium with magnesium, Lampl, E., *et al.*, (*ESA*) A.139
Neuromuscular block, recovery, Can repetition of high frequencies stimuli alter the value of 50 and 100 Hz tetanic fade during vecuronium induced neuromuscular blockade? Baurain, M. J., *et al.*, (*ESA*) A.135
——, Comparison between double-burst stimulation and 50, 100 Hz tetanic fade during spontaneous recovery of vecuronium induced neuromuscular blockade, Baurain, M. J., *et al.*, (*ESA*) A.133
——, Neostigmine antagonism of neuromuscular blockade induced by mivacurium, vecuronium and atracurium, Dernovoi, B. S., *et al.*, (*ESA*) A.137
Neuromuscular block, rocuronium, Concentration–effect relationship at the vocal cords and the adductor pollicis following rocuronium administration, Plaud, B., *et al.*, (*ESA*) A.141
——, The pharmacokinetics of rocuronium in pediatric patients: a pooled data analysis, Meistelman, C., *et al.*, (*ESA*) A.138
Neuromuscular block, vecuronium, Can repetition of high frequencies stimuli alter the value of 50 and 100 Hz tetanic fade during vecuronium induced neuromuscular blockade? Baurain, M. J., *et al.*, (*ESA*) A.135
——, Comparison between double-burst stimulation and 50, 100 Hz tetanic fade during spontaneous recovery of vecuronium induced neuromuscular blockade, Baurain, M. J., *et al.*, (*ESA*) A.133
——, Neostigmine antagonism of neuromuscular blockade induced by mivacurium, vecuronium and atracurium, Dernovoi, B. S., *et al.*, (*ESA*) A.137
——, Reversal of vecuronium induced neuromuscular blockade: No effects of atropine administration timing, Baurain, M. J., *et al.*, (*ESA*) A.134
——, Supra-additivity between atracurium and vecuronium, Meretoja, O. A., *et al.*, (*ESA*) A.140

Oxygen, consumption, Changes in blood lactate, total body oxygen delivery and consumption during liver transplantation, Carrera, J., *et al.*, (*ESA*) A.77
——, Influence of N-acetylcysteine on O_2 consumption and gastric intramucosal pH in septic patients, Spies, C., *et al.*, (*ESA*) A.186
——, Oxygen consumption is dependent upon oxygen delivery in cirrhotics undergoing liver transplantation, Piccinni, P., *et al.*, (*ESA*) A.78
——, The effect of dobutamine and norepinephrine on global and splanchnic O_2 consumption, Meier-Hellmann, A., *et al.*, (*ESA*) A.185
Oxygen, delivery systems, Extracorporeal membrane oxygenation for postoperative cardiac support in newborn infants: first clinical data, Marcassa, A., *et al.*, (*ESA*) A.168
Oxygen, saturation, Continuous monitoring of Sp_{O_2} during total intravenous anaesthesia with ketamine and spontaneous ventilation, Joly, L.-M., *et al.*, (*ESA*) A.58
——, Hypoxic events after general anaesthesia in the recovery room, Degasperi, D., *et al.*, (*ESA*) A.59
——, Influence of anaesthesia on post-operative hypoxaemia, Georgiou, L., *et al.*, (*ESA*) A.60
——, Jugular bulb metabolic monitoring during hyperventilation in severe head trauma patients, De Deyne, C., *et al.*, (*ESA*) A.106
Oxygen, tissue, Influence of norepinephrine therapy on the oxygen supply and lactate extraction rate of the liver in the septic pig, Schäfer, R., *et al.*, (*ESA*) A.184
——, Oxygen consumption is dependent upon oxygen delivery in cirrhotics undergoing liver transplantation, Piccinni, P., *et al.*, (*ESA*) A.78
——, The effect of dobutamine and norepinephrine on global and splanchnic O_2 consumption, Meier-Hellmann, A., *et al.*, (*ESA*) A.185
Oxygen, transport, The effect of dobutamine and norepinephrine on global and splanchnic O_2 consumption, Meier-Hellmann, A., *et al.*, (*ESA*) A.185
Oxygen, uptake, Propofol (2,6 diisopropylphenol) as an antioxidant *in-vitro*: a dose response study, Bennett, S., *et al.*, (*ESA*) A.152
——, Septic shock: effect of a goal-directed therapy on oxygen metabolism and serum cytokine levels, Martin, C., *et al.*, (*ESA*) A.189

Pain, acute, Intranasal fentanyl for breakthrough cancer pain or incident pain, Striebel, W. H., *et al.*, (*ESA*) A.210
——, Organization of acute pain services—a low-cost model, Rawal, N., (*ESA*) A.199
Pain, chronic, Diaphragmatic function after bupivacaine cervical extradural analgesia for chronic pain therapy, Nyström, E., *et al.*, (*ESA*) A.65
——, High dose oral morphine in cancer pain management, Radbruch, L., *et al.*, (*ESA*) A.212
——, Intranasal fentanyl for breakthrough cancer pain or incident pain, Striebel, W. H., *et al.*, (*ESA*) A.210
——, Intrathecal pain relief in terminally ill cancer patients at home, Wagemans, M. F. M., *et al.*, (*ESA*) A.213
——, Treatment of cancer pain with morphine (MO)—A double blind study of extradural (ED) *versus* intramuscular (im) routes of administration, Nath, S., *et al.*, (*ESA*) A.211
Pain, injection, Alizapride does reduce pain on injection of propofol: comparison with lidocaine, Zaouk, G., *et al.*, (*ESA*) A.11
——, Quality of Induction: a clinical comparison of Etomidat-Lipuro® and Hypnomidate®, Wiebalck, A., *et al.*, (*ESA*) A.154
Pain, mechanism, Differential effects of specific delta and kappa opioid antagonists on the bidirectionnal effect of naloxone in arthritic rats, Cattaneo, I., *et al.*, (*ESA*) A.114
Pain, postoperative, A survey of sleep problems in surgical patients, Beydon, L., *et al.*, (*ESA*) A.4

——, Addition of droperidol to PCA morphine: what is the optimal dose? Lamond, C. T., *et al.*, (*ESA*) A.204
——, Analgesia by wound infiltration before or after surgery in inguinal herniorraphy, Hennart, D., *et al.*, (*ESA*) A.202
——, Effect of morphine on a nociceptive flexion reflex in patients with postoperative pain, Chauvin, M., *et al.*, (*ESA*) A.115
——, Epidural administration of liposomal bupivacaine for the management of postsurgical pain, Boogaerts, J., *et al.*, (*ESA*) A.200
——, Epidural clonidine analgesia after major gynaecological surgery, Smilov, I., *et al.*, (*ESA*) A.176
——, Evaluation of pain and analgesia in a postanesthesia care unit, Aubrun, F., *et al.*, (*ESA*) A.198
——, Intranasal fentanyl for postoperative pain management in an unselected population, Striebel, W. H., *et al.*, (*ESA*) A.209
——, Organization of acute pain services—a low-cost model, Rawal, N., (*ESA*) A.199
——, Postoperative analgesia: a two dosage regimens trial for i.m. morphine after early i.v. titration, Butscher, K., *et al.*, (*ESA*) A.201
——, Preemptive analgesia with epidural morphine, Nègre, I., *et al.*, (*ESA*) A.203
Parasympathetic nervous system, atropine, Reversal of vecuronium induced neuromuscular blockade: No effects of atropine administration timing, Baurain, M. J., *et al.*, (*ESA*) A.134
Partial pressure, arterial–end-tidal, Relationship between arterial $P\text{CO}_2$ (Pa_{CO_2}) and end tidal CO_2 (ETCO_2) recorded through a laryngeal mask (LMA) in children breathing spontaneously, Van Obbergh, L. J., *et al.*, (*ESA*) A.164
Partial pressure, carbon dioxide, Is correlation of arterial and end-tidal carbon dioxide pressure during inhalation anaesthesia better with laryngeal mask as compared to face mask? Ivens, D., *et al.*, (*ESA*) A.17
Partial pressure, oxygen, Early postperfusion assessment of gas exchange and postoperative extubation outcome following coronary artery surgery, Knapik, P., *et al.*, (*ESA*) A.61
Pharmacodynamics, Concentration–effect relationship at the vocal cords and the adductor pollicis following rocuronium administration, Plaud, B., *et al.*, (*ESA*) A.141
——, Monitoring the onset of neuromuscular blockade at the orbicularis oculi can predict good intubating conditions when using 2 × ED_{95} of atracurium, Debaene, B., *et al.*, (*ESA*) A.142
——, Neuromuscular blockade following mivacurium in children during N_2O–halothane, Orliaguet, G., *et al.*, (*ESA*) A.163
Pharmacokinetics, alfentanil, Pharmacokinetic behaviour of transdermal fentanyl, Van Bastelaere, M., *et al.*, (*ESA*) A.146
——, Pharmacokinetics and effects of i.m. alfentanil as premedication for outpatient cataract surgery, Ali-Melkkilä, T., *et al.*, (*ESA*) A.145
Pharmacokinetics, bupivacaine, Slow-release effect of pH-adjusted bupivacaine: pharmacokinetic demonstration, Benhamou, D., *et al.*, (*ESA*) A.120
Pharmacokinetics, fentanyl, Pharmacokinetics of intranasal fentanyl, Striebel, H. W., *et al.*, (*ESA*) A.208
Pharmacokinetics, glycine, Glycine and its metabolites during and after intrauterine YAG laser surgery, Van Boven, M. J., *et al.*, (*ESA*) A.87
Pharmacokinetics, lung, Sufentanil first-pass pulmonary uptake at three different steady state concentrations of the drug, Boer, F., *et al.*, (*ESA*) A.147
Pharmacokinetics, midazolam, Midazolam premedication: a forensic approach to pharmacokinetics and amnesia, Motsch, J., *et al.*, (*ESA*) A.155
——, Prolonged (> 1 week) sedation with midazolam in ICU patients: efficacy, safety and pharmacokinetics, Heytens, L., *et al.*, (*ESA*) A.178
Pharmacokinetics, propofol, Pharmacokinetics of propofol and its conjugates after continuous infusion in normal and renal failure patients, Nathan, N., *et al.*, (*ESA*) A.151
Pharmacokinetics, rocuronium, Concentration–effect relationship at the vocal cords and the adductor pollicis following rocuronium administration, Plaud, B., *et al.*, (*ESA*) A.141
——, The pharmacokinetics of rocuronium in pediatric patients: a pooled data analysis, Meistelman, C., *et al.*, (*ESA*) A.138
Pharmacokinetics, uptake, Sufentanil first-pass pulmonary uptake at three different steady state concentrations of the drug, Boer, F., *et al.*, (*ESA*) A.147
——, The pharmacokinetics of rocuronium in pediatric patients: a pooled data analysis, Meistelman, C., *et al.*, (*ESA*) A.138
Pharmacology, 5-HT antagonists, Comparison of ondansetron, metoclopramide and droperidol for the prophylaxis of emetic symptoms after gynecological laparoscopic procedures, Geiger, C., *et al.*, (*ESA*) A.14
——, Double-blind comparison of ondansetron, droperidol and saline for prevention of nausea & vomiting after orthopaedic surgery, Gan, T. J., *et al.*, (*ESA*) A.13
——, Ondansetron 4 mg *vs* droperidol 1.25 mg in the prophylaxis of postoperative nausea and vomiting after alfentanil-supplemented inhalation anaesthesia, Alon, E., *et al.*, (*ESA*) A.12
Pharmacology, alizapride, Alizapride does reduce pain on injection of propofol: comparison with lidocaine, Zaouk, G., *et al.*, (*ESA*) A.11
Pharmacology, bupivacaine, Motor blockade and absence of local nerve toxicity induced by liposomal bupivacaine injected into the axillary brachial plexus of rabbits, Legros, F. J., *et al.*, (*ESA*) A.122
Pharmacology, captopril, Does captopril modify the arterial response to vasopressor substances? Le Pelley, E., *et al.*, (*ESA*) A.48
Pharmacology, clonidine, Clonidine in paediatric caudal anaesthesia, Jamali, S., *et al.*, (*ESA*) A.160
——, Effects of epidural clonidine on anaesthetic requirements and postoperative analgesia, Samsó, E., *et al.*, (*ESA*) A.205
——, Epidural clonidine and myocardial ischaemia after abdominal aortic surgery, Fulgencio, J. P., *et al.*, (*ESA*) A.42
——, Preoperative clonidine improves postoperative renal function in CABG patients, Kulka, P. J., *et al.*, (*ESA*) A.143
Pharmacology, dexmedetomidine, Dexmedetomidine does not exercise its anesthetic action through GABA, Salonen, M., *et al.*, (*ESA*) A.113
Pharmacology, dose–response, Propofol (2,6 diisopropylphenol) as an antioxidant *in-vitro*: a dose response study, Bennett, S., *et al.*, (*ESA*) A.152
Pharmacology, guanfacine, Effects of oral preoperative guanfacine on anesthetics requirements, Engelman, E., *et al.*, (*ESA*) A.144
Pharmacology, lemakalim, Lemakalim reverses ventricular conduction impairment induced by a large dose of bupivacaine in anesthetized dogs, de La Coussaye, J. E., *et al.*, (*ESA*) A.121
Pharmacology, morphine, Treatment of cancer pain with morphine (MO)—A double blind study of extradural (ED) *versus* intramuscular (im) routes of administration, Nath, S., *et al.*, (*ESA*) A.211
Pharmacology, N-acetylcysteine, Influence of N-acetylcysteine on O_2 consumption and gastric intramucosal pH in septic patients, Spies, C., *et al.*, (*ESA*) A.186
Pharmacology, preservatives, Functional recovery after 24 h preservation of rabbit hearts in University Wisconsin solution, Fellahi, J. L., *et al.*, (*ESA*) A.44
Pharmacology, propofol, Propofol (2,6 diisopropylphenol) as an antioxidant *in-vitro*: a dose response study, Bennett, S., *et al.*, (*ESA*) A.152
Pharmacology, synergism, Dexmedetomidine does not exercise its anesthetic action through GABA, Salonen, M., *et al.*, (*ESA*) A.113
——, Does exogenous dopamine reverse cardiovascular depression induced by isoflurane during thoracic epidural blockade? Raner, C., *et al.*, (*ESA*) A.49
——, Supra-additivity between atracurium and vecuronium, Meretoja, O. A., *et al.*, (*ESA*) A.140
Pig, Aprotinin does not decrease surgical bleeding and could promote arterial thrombosis in the pig: A prospective randomized, blind, study, Samama, C. M., *et al.*, (*ESA*) A.100
——, Does captopril modify the arterial response to vasopressor substances? Le Pelley, E., *et al.*, (*ESA*) A.48
——, Influence of cervicothoracic epidural anaesthesia (C-TEA) on left ventricular (LV) contractility—an experimental study in pigs with autonomous blockade, Reiz, S., *et al.*, (*ESA*) A.52
——, Influence of norepinephrine therapy on the oxygen supply and lactate extraction rate of the liver in the septic pig, Schäfer, R., *et al.*, (*ESA*) A.184
——, Midazolam prevents ketamine-induced stimulation of cerebral metabolism, Åkeson, J., *et al.*, (*ESA*) A.111
——, Pre- and intraoperative prevention by β-blockers, propranolol and esmolol, of ischaemia-induced ventricular fibrillation, Freysz, M., *et al.*, (*ESA*) A.46
Polypeptides, aprotinin, Aprotinin does not decrease surgical bleeding and could promote arterial thrombosis in the pig: A prospective randomized, blind, study, Samama, C. M., *et al.*, (*ESA*) A.100
——, Blood requirements reduction in orthotopic liver

transplantation with aprotinin, Monedero, P., *et al.*, (*ESA*) A.98

——, High dose aprotinin *versus* desmo-pressin acetate treatment in cardiac surgery, Hidalgo, F., *et al.*, (*ESA*) A.99

——, Use of aprotinine during cytoreductive surgery of ovarian cancer, Lequeau, F., *et al.*, (*ESA*) A.97

Polypeptides, cytokines, Molecular mediators and cardiac surgery, Pérez Arancón, J. L., *et al.*, (*ESA*) A.188

——, Molecular mediators and post-bacteraemic phase, Martínez Urionabarrenetxea, K., *et al.*, (*ESA*) A.187

——, Septic shock: effect of a goal-directed therapy on oxygen metabolism and serum cytokine levels, Martin, C., *et al.*, (*ESA*) A.189

Polypeptides, endothelin, Is the vasoconstrictive effect of cyclosporine mediated by endothelin in kidney transplantation? Mouquet, C., *et al.*, (*ESA*) A.84

Position, effects, Influence of pneumoperitoneum and posture on hemodynamic and stress responses during anaesthesia for laparoscopic surgery, Odeberg, S., *et al.*, (*ESA*) A.34

——, Influence of posture on the respiratory mechanics during anesthesia, Engelman, E., *et al.*, (*ESA*) A.56

Position, head, Influence of posture on the respiratory mechanics during anesthesia, Engelman, E., *et al.*, (*ESA*) A.56

Position, prone, The respiratory compliance in normal and obese subjects during anaesthesia, Mulazzi, D., *et al.*, (*ESA*) A.54

Position, supine, The respiratory compliance in normal and obese subjects during anaesthesia, Mulazzi, D., *et al.*, (*ESA*) A.54

Potency, anaesthetic, Addition of droperidol to PCA morphine: what is the optimal dose? Lamond, C. T., *et al.*, (*ESA*) A.204

——, Propofol (2,6 diisopropylphenol) as an antioxidant *in-vitro*: a dose response study, Bennett, S., *et al.*, (*ESA*) A.152

Potency, anaesthetic, MAC, Isoproterenol reverses the MAC decreasing effect of esmolol in rats, Perel, A., *et al.*, (*ESA*) A.117

Potency, drug, tolerance, Prolonged (> 1 week) sedation with midazolam in ICU patients: efficacy, safety and pharmacokinetics, Heytens, L., *et al.*, (*ESA*) A.178

Pregnancy, Neonatal glycemia: does the maternal i.v. fluid regimen during labor make a difference? Menigaux, C., *et al.*, (*ESA*) A.175

Premedication, Pharmacokinetics and effects of i.m. alfentanil as premedication for outpatient cataract surgery, Ali-Melkkilä, T., *et al.*, (*ESA*) A.145

Premedication, clonidine, Preoperative clonidine improves postoperative renal function in CABG patients, Kulka, P. J., *et al.*, (*ESA*) A.143

Premedication, guanfacine, Effects of oral preoperative guanfacine on anesthetics requirements, Engelman, E., *et al.*, (*ESA*) A.144

Premedication, midazolam, Dose dependent effects of oral medication with midazolam, Biro, P., *et al.*, (*ESA*) A.156

——, Midazolam premedication: a forensic approach to pharmacokinetics and amnesia, Motsch, J., *et al.*, (*ESA*) A.155

Premedication, nifedipine, Effect of premedication with nifedipine on intraoperative hypothermia, Vassilieff, N., *et al.*, (*ESA*) A.71

Protein, amino acids, Glycine and its metabolites during and after intrauterine YAG laser surgery, Van Boven, M. J., *et al.*, (*ESA*) A.87

Protein, globulin, Carbohydrate deficient transferrin: a new copredictor of alcoholism related postoperative complications? Heil, T., *et al.*, (*ESA*) A.88

Protein, metabolism, Effect of recombinant human growth hormone (HGH) on protein metabolism in surgical patients, Carli, F., *et al.*, (*ESA*) A.86

Psychological responses, Dose dependent effects of oral medication with midazolam, Biro, P., *et al.*, (*ESA*) A.156

Rabbit, Effects of hypertonic saline on coronary blood flow and myocardial performance of a blood-perfused, isolated rabbit heart, Delayance, S., *et al.*, (*ESA*) A.45

——, Functional recovery after 24 h preservation of rabbit hearts in University Wisconsin solution, Fellahi, J. L., *et al.*, (*ESA*) A.44

——, Motor blockade and absence of local nerve toxicity induced by liposomal bupivacaine injected into the axillary brachial plexus of rabbits, Legros, F. J., *et al.*, (*ESA*) A.122

——, Slow-release effect of pH-adjusted bupivacaine: pharmacokinetic demonstration, Benhamou, D., *et al.*, (*ESA*) A.120

Rat, Dexmedetomidine does not exercise its anesthetic action through GABA, Salonen, M., *et al.*, (*ESA*) A.113

——, Differential effects of specific delta and kappa opioid antagonists on the bidirectionnal effect of naloxone in arthritic rats, Cattaneo, I., *et al.*, (*ESA*) A.114

——, Involvement of μ, δ, and κ receptors in the inhibition by intrathecal morphine of a C-fibre evoked reflex in the rat, Guirimand, F., *et al.*, (*ESA*) A.116

——, Isoproterenol reverses the MAC decreasing effect of esmolol in rats, Perel, A., *et al.*, (*ESA*) A.117

——, Nitrous oxide induced neuronal depression: modification through benzodiazepine receptors, Dzoljic, M., *et al.*, (*ESA*) A.112

Receptors, opioid, Differential effects of specific delta and kappa opioid antagonists on the bidirectionnal effect of naloxone in arthritic rats, Cattaneo, I., *et al.*, (*ESA*) A.114

——, Involvement of μ, δ, and κ receptors in the inhibition by intrathecal morphine of a C-fibre evoked reflex in the rat, Guirimand, F., *et al.*, (*ESA*) A.116

Records, A national database for intensive care medicine in Sweden, Karling, M., (*ESA*) A.8

Recovery, Flumazenil facilitates intraoperative arousal in scoliosis surgery, Koscielniak-Nielsen, Z. J., *et al.*, (*ESA*) A.157

Recovery, postoperative, Hypoxic events after general anaesthesia in the recovery room, Degasperi, D., *et al.*, (*ESA*) A.59

Recovery, psychomotor, Evaluation of saccadic eye movements as an objective test during recovery from anesthesia, Paut, O., *et al.*, (*ESA*) A.10

Reflexes, spinal, Effect of morphine on a nociceptive flexion reflex in patients with postoperative pain, Chauvin, M., *et al.*, (*ESA*) A.115

——, Involvement of μ, δ, and κ receptors in the inhibition by intrathecal morphine of a C-fibre evoked reflex in the rat, Guirimand, F., *et al.*, (*ESA*) A.116

Safety, drug, Diamorphine/bupivacaine mixture *vs* plain bupivacaine: a comparison of epidural infusions in labour, Bailey, C. R., *et al.*, (*ESA*) A.169

——, Dose dependent effects of oral medication with midazolam, Biro, P., *et al.*, (*ESA*) A.156

——, High dose oral morphine in cancer pain management, Radbruch, L., *et al.*, (*ESA*) A.212

——, Motor blockade and absence of local nerve toxicity induced by liposomal bupivacaine injected into the axillary brachial plexus of rabbits, Legros, F. J., *et al.*, (*ESA*) A.122

——, Prolonged (> 1 week) sedation with midazolam in ICU patients: efficacy, safety and pharmacokinetics, Heytens, L., *et al.*, (*ESA*) A.178

Safety, equipment, Computer-controlled syringe pump improves safety of pharmacokinetic models, Duranteau, R., *et al.*, (*ESA*) A.148

Safety, techniques, Abdominal wall retraction may decrease anaesthesiological risks of laparoscopic cholecystectomy, Vereczkey, Z., *et al.*, (*ESA*) A.64

——, Continuous monitoring of Sp_{O_2} during total intravenous anaesthesia with ketamine and spontaneous ventilation, Joly, L.-M., *et al.*, (*ESA*) A.58

——, Diaphragmatic function after bupivacaine cervical extradural analgesia for chronic pain therapy, Nyström, E., *et al.*, (*ESA*) A.65

——, EEG-monitoring during defibrillator-implantation: effects of repetitive cerebral ischemia on electric brain activity, Spies, C., *et al.*, (*ESA*) A.110

——, Effects of postoperative auto-transfusion in spine surgery, Riou, B., *et al.*, (*ESA*) A.103

——, External ventricular CSF drains infections, Mahé, V., *et al.*, (*ESA*) A.109

——, Fentanyl or buprenorphine side effects in spinal anaesthesia, Foppoli, R, *et al.*, (*ESA*) A.132

——, Flumazenil facilitates intraoperative arousal in scoliosis surgery, Koscielniak-Nielsen, Z. J., *et al.*, (*ESA*) A.157

——, Intrathecal pain relief in terminally ill cancer patients at home, Wagemans, M. F. M., *et al.*, (*ESA*) A.213

——, Jugular bulb metabolic monitoring during hyperventilation in severe head trauma patients, De Deyne, C., *et al.*, (*ESA*) A.106

——, Propofol anaesthesia with spontaneous breathing for extracorporeal shock wave lithotripsy, Pasch, T., *et al.*, (*ESA*) A.153

——, Respiratory effects of laparoscopic cholecystectomy (preliminary data), Crea, M. A., *et al.*, (*ESA*) A.63

——, Safety of PCA in elderly, Santangelo, E., *et al.*, (*ESA*) A.206

——, Use of thoracic epidural block for perioperative analgesia in children, Entress, A. H., *et al.*, (*ESA*) A.158

Scoliosis, Flumazenil facilitates intraoperative arousal in scoliosis surgery, Koscielniak-Nielsen, Z. J., *et al.*, (*ESA*) A.157

Screening, A new clinical score to predict difficult intubation, Arné, J., *et al.*, (*ESA*) A.1

——, Carbohydrate deficient transferrin: a new copredictor of alcoholism related postoperative complications? Heil, T., *et al.*, (*ESA*) A.88

——, Dipyridamole-TEE and 24 h Holter-ECG as preoperative screening tests for coronary artery disease in patients with abdominal aortic aneurysm, Östman, M., *et al.*, (*ESA*) A.22

——, Does routine preoperative coronary angiography modify outcome after aortic surgery? Gosgnach, M., *et al.*, (*ESA*) A.6

——, Indications for coronary revascularisation in vascular surgical patients, Gosgnach, M., *et al.*, (*ESA*) A.5

——, Molecular mediators and cardiac surgery, Pérez Arancón, J. L., *et al.*, (*ESA*) A.188

——, Molecular mediators and post-bacteraemic phase, Martínez Urionabarrenetxea, K., *et al.*, (*ESA*) A.187

Sedation, A comparison of midazolam and midazolam plus fentanyl for colonoscopy, Dupont, H., *et al.*, (*ESA*) A.9

——, Dose dependent effects of oral medication with midazolam, Biro, P., *et al.*, (*ESA*) A.156

——, Target-controlled intravenous sedation with propofol, Mergaert, C., *et al.*, (*ESA*) A.149

Sleep, A survey of sleep problems in surgical patients, Beydon, L., *et al.*, (*ESA*) A.4

Sleep apnoea, Cerebral perfusion during obstructive sleep apnea (OSA), Bålfors, E., *et al.*, (*ESA*) A.62

Spinal cord, evoked potentials, Involvement of μ, δ, and κ receptors in the inhibition by intrathecal morphine of a C-fibre evoked reflex in the rat, Guirimand, F., *et al.*, (*ESA*) A.116

Spinal cord, GABA, Dexmedetomidine does not exercise its anesthetic action through GABA, Salonen, M., *et al.*, (*ESA*) A.113

Spinal cord, motor block, Effects of intrathecal meperidine (MP), fentanyl (FN) and lidocaine (LD) on somatosensory (SSEP) and cortical motor (CMEP) evoked potentials in humans, Fernandez, S., *et al.*, (*ESA*) A.119

Spinal cord, sensory block, Effects of intrathecal meperidine (MP), fentanyl (FN) and lidocaine (LD) on somatosensory (SSEP) and cortical motor (CMEP) evoked potentials in humans, Fernandez, S., *et al.*, (*ESA*) A.119

Statistics, A national database for intensive care medicine in Sweden, Karling, M., (*ESA*) A.8

Stress, Influence of pneumoperitoneum and posture on hemodynamic and stress responses during anaesthesia for laparoscopic surgery, Odeberg, S., *et al.*, (*ESA*) A.34

Surgery, abdominal, Postoperative hypoxaemia: comparison of epidural and patient controlled analgesia, Spencer, A., *et al.*, (*ESA*) A.207

Surgery, aneurysm, Effects of oral preoperative guanfacine on anesthetics requirements, Engelman, E., *et al.*, (*ESA*) A.144

——, Influence of positive pressure ventilation on myocardial ischaemia after abdominal aortic aneurysm repair, McCoy, D., *et al.*, (*ESA*) A.43

Surgery, cardiovascular, Accuracy of processed auditory evoked response in predicting movement during cardiac surgery, Kuppe, H., *et al.*, (*ESA*) A.31

——, Acute preoperative plasmapheresis during cardiac surgery, Armellin, G., *et al.*, (*ESA*) A.104

——, Cardiac output determined from pulmonary gas exchange, Österlund, B., *et al.*, (*ESA*) A.19

——, Comparison of dobutamine with enoximone following open heart surgery in small children, Innes, P., *et al.*, (*ESA*) A.167

——, Early postperfusion assessment of gas exchange and postoperative extubation outcome following coronary artery surgery, Knapik, P., *et al.*, (*ESA*) A.61

——, Extracorporeal membrane oxygenation for postoperative cardiac support in newborn infants: first clinical data, Marcassa, A., *et al.*, (*ESA*) A.168

——, High dose aprotinin *versus* desmo-pressin acetate treatment in cardiac surgery, Hidalgo, F., *et al.*, (*ESA*) A.99

——, Molecular mediators and cardiac surgery, Pérez Arancón, J. L., *et al.*, (*ESA*) A.188

——, Pulmonary and systemic vascular effects of isoproterenol, nitroglycerin and prostaglandin E1 early after cardiac operations in patients with pulmonary hypertension, Alvarez, J., *et al.*, (*ESA*) A.27

——, The combined prophylactic administration of H1 and H2 receptor blockers in the prevention of protamine related haemodynamic effects and the relation between antihistaminics-leucocytes and pulmonary vascular resistance, Durak, P., *et al.*, (*ESA*) A.95

——, The relationship between cardiopulmonary bypass related immunologic effects and complement, thromboxane and leucocyte parameters, Durak, P., *et al.*, (*ESA*) A.96

——, Tolerance of preoperative transesophageal echocardiography in patients scheduled for aortic surgery, Gosgnach, M., *et al.*, (*ESA*) A.21

Surgery, cataract, Pharmacokinetics and effects of i.m. alfentanil as premedication for outpatient cataract surgery, Ali-Melkkilä, T., *et al.*, (*ESA*) A.145

Surgery, cleft palate, Evaluation of a forced-air warmer (Bair-Hugger) in maintaining body temperature in infants during cleft palate surgery, Murat, I., *et al.*, (*ESA*) A.166

Surgery, day-case, Pharmacokinetics and effects of i.m. alfentanil as premedication for outpatient cataract surgery, Ali-Melkkilä, T., *et al.*, (*ESA*) A.145

Surgery, endoscopy, A comparison of midazolam and midazolam plus fentanyl for colonoscopy, Dupont, H., *et al.*, (*ESA*) A.9

Surgery, gastrointestinal, Abdominal wall retraction may decrease anaesthesiological risks of laparoscopic cholecystectomy, Vereczkey, Z., *et al.*, (*ESA*) A.64

——, Influence of pneumoperitoneum and posture on hemodynamic and stress responses during anaesthesia for laparoscopic surgery, Odeberg, S., *et al.*, (*ESA*) A.34

——, Neuroendocrine changes during pneumoperitoneum for laparoscopic cholecystectomy, Joris, J., *et al.*, (*ESA*) A.33

——, Respiratory effects of laparoscopic cholecystectomy (preliminary data), Crea, M. A., *et al.*, (*ESA*) A.63

Surgery, gynaecological, An audit of the incidence and costs associated with post operative nausea and vomiting (PONV) following major gynaecological surgery in an inpatient population, Morris, R. W., *et al.*, (*ESA*) A.2

——, Cerebral blood flow velocities (CBFV) during anaesthesia for gynaecological laparoscopic surgery, Granry, J. C., *et al.*, (*ESA*) A.32

——, Comparison of ondansetron, metoclopramide and droperidol for the prophylaxis of emetic symptoms after gynecological laparoscopic procedures, Geiger, C., *et al.*, (*ESA*) A.14

——, Epidural clonidine analgesia after major gynaecological surgery, Smilov, I., *et al.*, (*ESA*) A.176

——, Glycine and its metabolites during and after intrauterine YAG laser surgery, Van Boven, M. J., *et al.*, (*ESA*) A.87

——, Ondansetron 4 mg *vs* droperidol 1.25 mg in the prophylaxis of postoperative nausea and vomiting after alfentanil-supplemented inhalation anaesthesia, Alon, E., *et al.*, (*ESA*) A.12

——, Sequential spinal peridural anaesthesia for gynaecological surgery under laparoscopy, Joos, S., *et al.*, (*ESA*) A.130

——, Use of aprotinine during cytoreductive surgery of ovarian cancer, Lequeau, F., *et al.*, (*ESA*) A.97

Surgery, hormonal response, Influence of pneumoperitoneum and posture on hemodynamic and stress responses during anaesthesia for laparoscopic surgery, Odeberg, S., *et al.*, (*ESA*) A.34

——, Neuroendocrine changes during pneumoperitoneum for laparoscopic cholecystectomy, Joris, J., *et al.*, (*ESA*) A.33

——, Volume loading and hormonal factors in the prevention of acute tubular necrosis in kidney transplantation, Mouquet, C., *et al.*, (*ESA*) A.83

Surgery, laparoscopy, Abdominal wall retraction may decrease anaesthesiological risks of laparoscopic cholecystectomy, Vereczkey, Z., *et al.*, (*ESA*) A.64

——, Influence of pneumoperitoneum and posture on hemodynamic and stress responses during anaesthesia for laparoscopic surgery, Odeberg, S., *et al.*, (*ESA*) A.34

——, Neuroendocrine changes during pneumoperitoneum for laparoscopic cholecystectomy, Joris, J., *et al.*, (*ESA*) A.33

——, Preoperative skin-surface warming reduces intraoperative hypothermia, Camus, Y., *et al.*, (*ESA*) A.72

——, Respiratory effects of laparoscopic cholecystectomy (preliminary data), Crea, M. A., *et al.*, (*ESA*) A.63

——, Sequential spinal peridural anaesthesia for gynaecological surgery under laparoscopy, Joos, S., *et al.*, (*ESA*) A.130

Surgery, laser, Glycine and its metabolites during and after intrauterine YAG laser surgery, Van Boven, M. J., *et al.*, (*ESA*) A.87

Surgery, metabolic response, Effect of recombinant human growth hormone (HGH) on protein metabolism in surgical patients, Carli, F., *et al.*, (*ESA*) A.86

Surgery, miscellaneous, A survey of sleep problems in surgical patients, Beydon, L., *et al.*, (*ESA*) A.4

——, Analgesia by wound infiltration before or after surgery in inguinal herniography, Hennart, D., *et al.*, (*ESA*) A.202

Surgery, neurological, Effect of esmolol *versus* lidocaine on intracranial pressure and haemodynamic responses to

laryngoscopy and intubation, Samaha, T., *et al.*, (*ESA*) A.118
——, Jugular bulb metabolic monitoring during hyperventilation in severe head trauma patients, De Deyne, C., *et al.*, (*ESA*) A.106
——, Sufentanil increases intracranial pressure in patients with head trauma, Albanese, J., *et al.*, (*ESA*) A.107
——, Transcranial Doppler sonography: effect of propofol and thiopental in patients with brain tumors and brain injuries, Schregel, W., *et al.*, (*ESA*) A.105
Surgery, ophthalmological, Priming of atracurium with magnesium, Lampl, E., *et al.*, (*ESA*) A.139
Surgery, orthopaedic, An investigation into the effect of passive and active cutaneous warming devices on intraoperative body temperature in elderly patients, Bennet, J., *et al.*, (*ESA*) A.73
——, Anesthesia for patients ≥ 90 years of age in emergency hip surgery, Eleftheriadis, S., *et al.*, (*ESA*) A.3
——, Double-blind comparison of ondansetron, droperidol and saline for prevention of nausea & vomiting after orthopaedic surgery, Gan, T. J., *et al.*, (*ESA*) A.13
——, Effectiveness of core warming on net transfer of body heat across the skin, Kulkarni, P., *et al.*, (*ESA*) A.70
——, Effects of recombinant-human erythropoietin on postoperative transfusion requirements in subjects undergoing major orthopaedic surgery, Faris, P. P., *et al.*, (*ESA*) A.101
——, Fentanyl or buprenorphine side effects in spinal anaesthesia, Foppoli, R, *et al.*, (*ESA*) A.132
——, Inhibition of increase of blood thromboxane concentration by acetylsalicylic acid after release of tourniquet in lower extremity operations, Ojanen, R., *et al.*, (*ESA*) A.94
Surgery, spinal, Effects of postoperative auto-transfusion in spine surgery, Riou, B., *et al.*, (*ESA*) A.103
——, Evaluation of the efficacy of forced-air warmer (Bair Hugger) during spinal surgery in children, Murat, I., *et al.*, (*ESA*) A.165
——, Flumazenil facilitates intraoperative arousal in scoliosis surgery, Koscielniak-Nielsen, Z. J., *et al.*, (*ESA*) A.157
——, Preoperative autotransfusion in emergency surgery for spine trauma, Riou, B., *et al.*, (*ESA*) A.102
Surgery, thyroidectomy, Day 0 or day 3 laryngoscopy after thyroidectomy? Lacoste, L., *et al.*, (*ESA*) A.67
——, Direct, indirect or flexible laryngoscopy after thyroidectomy? Lacoste, L., *et al.*, (*ESA*) A.66
Surgery, transplantation, Changes in blood lactate, total body oxygen delivery and consumption during liver transplantation, Carrera, J., *et al.*, (*ESA*) A.77
——, Measurement of sigmoid intramural pH during orthotopic liver transplantation, Auroy, Y., *et al.*, (*ESA*) A.76
——, Modification of the renin–aldosterone axis during orthotopic liver transplantation, De los Ríos, J., *et al.*, (*ESA*) A.75
——, Oxygen consumption is dependent upon oxygen delivery in cirrhotics undergoing liver transplantation, Piccinni, P., *et al.*, (*ESA*) A.78
Surgery, urological, Propofol anaesthesia with spontaneous breathing for extracorporeal shock wave lithotripsy, Pasch, T., *et al.*, (*ESA*) A.153
Surgery, vascular, Determinants of systolic pressure variation in patients ventilated after vascular surgery, Beaussier, M., *et al.*, (*ESA*) A.37
——, Does routine preoperative coronary angiography modify outcome after aortic surgery? Gosgnach, M., *et al.*, (*ESA*) A.6
——, Effects of nitrous oxide (N_2O) on systemic haemodynamics, regional left ventricular (LV) function and incidence of myocardial ischaemia (MI) in vascular surgical patients with coronary artery disease (CAD), Hohner, P., *et al.*, (*ESA*) A.41
——, Effects of oral preoperative guanfacine on anesthetics requirements, Engelman, E., *et al.*, (*ESA*) A.144
——, Epidural clonidine and myocardial ischaemia after abdominal aortic surgery, Fulgencio, J. P., *et al.*, (*ESA*) A.42
——, Indications for coronary revascularisation in vascular surgical patients, Gosgnach, M., *et al.*, (*ESA*) A.5
——, The systolic pressure variation predicts response to volume loading in patients ventilated after aortic surgery, Coriat, P., *et al.*, (*ESA*) A.38
Sympathetic nervous system, clonidine, Effects of epidural clonidine on anaesthetic requirements and postoperative analgesia, Samsó, E., *et al.*, (*ESA*) A.205
——, Epidural clonidine analgesia after major gynaecological surgery, Smilov, I., *et al.*, (*ESA*) A.176
——, Epidural clonidine and myocardial ischaemia after abdominal aortic surgery, Fulgencio, J. P., *et al.*, (*ESA*) A.42
Sympathetic nervous system, dexmedetomidine, Dexmedetomidine does not exercise its anesthetic action through GABA, Salonen, M., *et al.*, (*ESA*) A.113
Sympathetic nervous system, dobutamine, The effect of dobutamine and norepinephrine on global and splanchnic O_2 consumption, Meier-Hellmann, A., *et al.*, (*ESA*) A.185
Sympathetic nervous system, dopamine, Does exogenous dopamine reverse cardiovascular depression induced by isoflurane during thoracic epidural blockade? Raner, C., *et al.*, (*ESA*) A.49
Sympathetic nervous system, ephedrine, Spinal anesthesia for C section: addition of phenylephrine to ephedrine for prevention of maternal hypotension, Thirion, A.-V., *et al.*, (*ESA*) A.172
Sympathetic nervous system, esmolol, Effect of esmolol *versus* lidocaine on intracranial pressure and haemodynamic responses to laryngoscopy and intubation, Samaha, T., *et al.*, (*ESA*) A.118
——, Isoproterenol reverses the MAC decreasing effect of esmolol in rats, Perel, A., *et al.*, (*ESA*) A.117
Sympathetic nervous system, isoprenaline, Isoproterenol reverses the MAC decreasing effect of esmolol in rats, Perel, A., *et al.*, (*ESA*) A.117
Sympathetic nervous system, noradrenaline, Influence of norepinephrine therapy on the oxygen supply and lactate extraction rate of the liver in the septic pig, Schäfer, R., *et al.*, (*ESA*) A.184
——, The effect of dobutamine and norepinephrine on global and splanchnic O_2 consumption, Meier-Hellmann, A., *et al.*, (*ESA*) A.185
Sympathetic nervous system, pharmacology, Does captopril modify the arterial response to vasopressor substances? Le Pelley, E., *et al.*, (*ESA*) A.48
Sympathetic nervous system, phenylephrine, Spinal anesthesia for C section: addition of phenylephrine to ephedrine for prevention of maternal hypotension, Thirion, A.-V., *et al.*, (*ESA*) A.172

Temperature, body, An investigation into the effect of passive and active cutaneous warming devices on intraoperative body temperature in elderly patients, Bennet, J., *et al.*, (*ESA*) A.73
——, Core–peripheral temperature difference in early *vs* later extubation after coronary artery surgery, Knapik, P., *et al.*, (*ESA*) A.69
——, Effect of premedication with nifedipine on intraoperative hypothermia, Vassilieff, N., *et al.*, (*ESA*) A.71
——, Effectiveness of core warming on net transfer of body heat across the skin, Kulkarni, P., *et al.*, (*ESA*) A.70
——, Evaluation of a forced-air warmer (Bair-Hugger) in maintaining body temperature in infants during cleft palate surgery, Murat, I., *et al.*, (*ESA*) A.166
——, Evaluation of the efficacy of forced-air warmer (Bair Hugger) during spinal surgery in children, Murat, I., *et al.*, (*ESA*) A.165
——, Preoperative skin-surface warming reduces intraoperative hypothermia, Camus, Y., *et al.*, (*ESA*) A.72
Temperature, regulation, Fentanyl, as pethidine, inhibits post anaesthesia shivering, Alfonsi, P., *et al.*, (*ESA*) A.74
Temperature, skin, An investigation into the effect of passive and active cutaneous warming devices on intraoperative body temperature in elderly patients, Bennet, J., *et al.*, (*ESA*) A.73
——, Preoperative skin-surface warming reduces intraoperative hypothermia, Camus, Y., *et al.*, (*ESA*) A.72
Theories of anaesthetic action, cellular mechanisms, Nitrous oxide induced neuronal depression: modification through benzodiazepine receptors, Dzoljic, M., *et al.*, (*ESA*) A.112
Thromboxane, Inhibition of increase of blood thromboxane concentration by acetylsalicylic acid after release of tourniquet in lower extremity operations, Ojanen, R., *et al.*, (*ESA*) A.94
——, The relationship between cardiopulmonary bypass related immunologic effects and complement, thromboxane and leucocyte parameters, Durak, P., *et al.*, (*ESA*) A.96
Toxicity, local anaesthetics, Motor blockade and absence of local nerve toxicity induced by liposomal bupivacaine injected into the axillary brachial plexus of rabbits, Legros, F. J., *et al.*, (*ESA*) A.122
Transfusion, Effects of recombinant-human erythropoietin on postoperative transfusion requirements in subjects undergoing major orthopaedic surgery, Faris, P. P., *et al.*, (*ESA*) A.101
Transfusion, autotransfusion, Acute preoperative

plasmapheresis during cardiac surgery, Armellin, G., *et al.*, (*ESA*) A.104
——, Effects of postoperative auto-transfusion in spine surgery, Riou, B., *et al.*, (*ESA*) A.103
——, Preoperative autotransfusion in emergency surgery for spine trauma, Riou, B., *et al.*, (*ESA*) A.102

Uterus, oxytocin, Mechanisms of ECG changes during caesarean section (CS)—a hypothesis, Svanström, M., *et al.*, (*ESA*) A.177

Veins, complications, Quality of Induction: a clinical comparison of Etomidat-Lipuro® and Hypnomidate®, Wiebalck, A., *et al.*, (*ESA*) A.154
Ventilation, hyperventilation, Jugular bulb metabolic monitoring during hyperventilation in severe head trauma patients, De Deyne, C., *et al.*, (*ESA*) A.106
Ventilation, mechanical, Comparison of pressure support ventilation provided by two ICU ventilators, Kalfon, P., *et al.*, (*ESA*) A.182
——, Continuous monitoring of the ventilatory mechanics during anaesthesia & intensive care, Py, C., *et al.*, (*ESA*) A.57
——, Determinants of systolic pressure variation in patients ventilated after vascular surgery, Beaussier, M., *et al.*, (*ESA*) A.37
——, Histology aspects of pulmonary barotrauma in critically ill patients with acute respiratory failure, Rouby, J. J., *et al.*, (*ESA*) A.181
——, Recruitment of atelectasis during general anaesthesia: a CT-study, Rothen, H. U., *et al.*, (*ESA*) A.53
——, The systolic pressure variation predicts response to volume loading in patients ventilated after aortic surgery, Coriat, P., *et al.*, (*ESA*) A.38
Ventilation, mechanics, Continuous monitoring of the ventilatory mechanics during anaesthesia & intensive care, Py, C., *et al.*, (*ESA*) A.57
——, Continuous spirometry: an aid in the intraoperative respiratory monitoring—case reports, Bardoczky, G., *et al.*, (*ESA*) A.55
——, Influence of posture on the respiratory mechanics during anesthesia, Engelman, E., *et al.*, (*ESA*) A.56
——, The respiratory compliance in normal and obese subjects during anaesthesia, Mulazzi, D., *et al.*, (*ESA*) A.54
Ventilation, positive end-expiratory pressure, Influence of positive pressure ventilation on myocardial ischaemia after abdominal aortic aneurysm repair, McCoy, D., *et al.*, (*ESA*) A.43
Ventilation, postoperative, Early postperfusion assessment of gas exchange and postoperative extubation outcome following coronary artery surgery, Knapik, P., *et al.*, (*ESA*) A.61
Ventilation, pressure support, Comparison of pressure support ventilation provided by two ICU ventilators, Kalfon, P., *et al.*, (*ESA*) A.182
Vomiting, antiemetics, Addition of droperidol to PCA morphine: what is the optimal dose? Lamond, C. T., *et al.*, (*ESA*) A.204
——, Alizapride does reduce pain on injection of propofol: comparison with lidocaine, Zaouk, G., *et al.*, (*ESA*) A.11
——, An audit of the incidence and costs associated with post operative nausea and vomiting (PONV) following major gynaecological surgery in an inpatient population, Morris, R. W., *et al.*, (*ESA*) A.2
——, Comparison of ondansetron, metoclopramide and droperidol for the prophylaxis of emetic symptoms after gynecological laparoscopic procedures, Geiger, C., *et al.*, (*ESA*) A.14
——, Double-blind comparison of ondansetron, droperidol and saline for prevention of nausea & vomiting after orthopaedic surgery, Gan, T. J., *et al.*, (*ESA*) A.13
——, Ondansetron 4 mg *vs* droperidol 1.25 mg in the prophylaxis of postoperative nausea and vomiting after alfentanil-supplemented inhalation anaesthesia, Alon, E., *et al.*, (*ESA*) A.12
Vomiting, nausea, Addition of droperidol to PCA morphine: what is the optimal dose? Lamond, C. T., *et al.*, (*ESA*) A.204
——, An audit of the incidence and costs associated with post operative nausea and vomiting (PONV) following major gynaecological surgery in an inpatient population, Morris, R. W., *et al.*, (*ESA*) A.2
——, Comparison of ondansetron, metoclopramide and droperidol for the prophylaxis of emetic symptoms after gynecological laparoscopic procedures, Geiger, C., *et al.*, (*ESA*) A.14
——, Double-blind comparison of ondansetron, droperidol and saline for prevention of nausea & vomiting after orthopaedic surgery, Gan, T. J., *et al.*, (*ESA*) A.13
——, Ondansetron 4 mg *vs* droperidol 1.25 mg in the prophylaxis of postoperative nausea and vomiting after alfentanil-supplemented inhalation anaesthesia, Alon, E., *et al.*, (*ESA*) A.12

Papers for publication and all editorial communications should be addressed to:
Professor G. Smith,
Editor, British Journal of Anaesthesia,
University Department of Anaesthesia,
Leicester Royal Infirmary,
Leicester LE1 5WW.
Telephone: 0533 470141
Fax: 0533 854487

All **business communications** should be sent to the Publishers: Professional & Scientific Publications Ltd, BMA House, Tavistock Square, London WC1H 9JR.

The GUIDE TO CONTRIBUTORS may be found in the advertisement section of this issue (pages ii, iv & vi).
Published monthly. Annual subscriptions: Worldwide £125.00; USA only $198.00 (direct orders only). Trainee rate: Worldwide £69.00. Airmail rates on application. ISSN 0007–0912. Orders must be accompanied by payment; cheques should be made payable to Professional and Scientific Publications. Orders and payments should be sent to Professional and Scientific Publications, BMA House, Tavistock Square, London WC1H 9JR. Orders in the United States of America may be sent to Professional and Scientific Publications, Box 560B, Kennebunkport, Maine 04046.

Group Advertisement Director, Mr R. Hayzen.
Advertisement Manager, Mr A. Allsop.
Publishing Manager, Mr D. Shaw.
BMA House, Tavistock Square, London WC1H 9JR. 071-387 4499.

Whilst every effort is made by the publishers and editorial committee to see that no inaccurate or misleading data, opinions or statement appear in this Journal, they wish to make it clear that the data and opinions appearing in the articles and advertisements herein are the responsibility of the contributor or advertiser concerned. Accordingly, the publishers and the editorial committee and their respective employees, officers and agents accept no liability whatsoever for the consequences of any such inaccurate or misleading data, opinions or statements. Whilst every effort is made to ensure that drug doses and other quantities are presented accurately, readers are advised that new methods and techniques involving drug usage, and described within this Journal, should only be followed in conjunction with the drug manufacturer's own published literature.

© Copyright: 1993 *British Journal of Anaesthesia*
All rights reserved. No part of this publication may be reproduced, stored in a retrieval system, or transmitted in any form by any means, electronic, mechanical, photocopying, recording or otherwise, without the prior permission of the *British Journal of Anaesthesia*, requests for which should be addressed to the **Editor**.

Published by Professional and Scientific Publications.
Printed in Great Britain by the University Press, Cambridge.

"I would have everie man write what he knowes and no more."—MONTAIGNE

BRITISH JOURNAL OF ANAESTHESIA

VOLUME 70, No. 1 JANUARY 1993

EDITORIAL I

HOW LONG SHOULD PATIENTS FAST BEFORE SURGERY? TIME FOR NEW GUIDELINES

"While it is desirable that there should be no solid matter in the stomach when chloroform is administered, it will be found very salutary to give a cup of tea or beef-tea about two hours previously." This sensible advice was given by Joseph, Baron Lister, in Holmes' *System of Surgery* in 1883. Why is the *British Journal of Anaesthesia* publishing a paper [1] in this issue, some 110 years later, offering the same advice but with an implication that this is something revolutionary? In the intervening years, concepts of "nil by mouth (or, in North American NPO) after midnight", or fluid restriction for a minimum period of time (usually 4–6 h, but many patients exceed this, encouraged by their doctors who believe longer is better), before an anaesthetic (either regional or general), have evolved. While none would argue that food should be ingested immediately before an anaesthetic, it is not clear where the idea of prolonged fluid restriction originated [2]. However, many anaesthetists assume that fluid deprivation protects patients against the risk of aspiration of acid gastric contents into the lungs, which may lead to the development of Mendelson's syndrome [3].

Mendelson [3] reviewed retrospectively the case notes of 44016 pregnancies in his hospital from 1932 to 1945. There were 66 cases of aspiration of stomach contents into the lungs (incidence 0.15%). In 45 cases, the aspirated material was recorded: 40 were liquid and, although the patients developed the characteristic chest radiograph changes which now bear Mendelson's name, there were no deaths; five patients inhaled solid material and died, in Mendelson's opinion from "suffocation". In the same paper, he showed elegantly that human acid vomitus injected into the trachea of rabbits caused the same chest radiograph changes he had observed in his patients. However, when he neutralized the vomitus, the radiographic changes did not occur. Solid material introduced into the rabbit's trachea caused either partial obstruction with ensuing massive atelectasis, or complete obstruction and suffocation. As a result of his observations, Mendelson offered the following advice in 1946: no oral feeding during labour—i.v. fluids should be given; wider use of local anaesthesia; alkalinization and emptying of the stomach before general anaesthesia; competent administration of general anaesthesia with full appreciation of the dangers of aspiration during induction and recovery; and the use of tracheal intubation. These tenets form the basis of obstetric anaesthesia today. A question remains, why did none of Mendelson's patients die after inhaling liquid acid gastric contents? In contrast, pregnant patients who inhaled liquid gastric contents in association with general anaesthesia and died have been detailed with depressing regularity by the triennial *Confidential Enquiry into Maternal Mortality* in Great Britain over the past 20 years; similarly, in non-pregnant adult patients and children, national and international surveys have described fatal pulmonary aspiration. However, it seems likely that these deaths relate more to the presence of risk factors such as gastrointestinal obstruction, head injury, depressed level of consciousness caused by drugs and repeated attempts at tracheal intubation and hypoxia with aspiration as a secondary event, or the use of positive pressure ventilation after aspiration, rather than to the acid material itself [4–7].

The next part of the story follows Mendelson's suggestion of alkalinizing the stomach. The availability of potent H_2 receptor blocking drugs [8] seemed the answer to the commonly quoted patient at risk of developing acid aspiration (Mendelson's) syndrome should they inhale their gastric contents, of a volume greater than 25 ml and pH less than 2.5, at induction of anaesthesia. It is worth noting that these figures are extrapolated from unpublished observations in Rhesus monkeys and cannot be tested ethically in humans. Nevertheless, most investigators have used these criteria of risk when assessing means of altering the gastric environment. Although H_2 receptor blockers are extremely effective in reducing gastric volume and increasing its pH, they do not produce this effect in every patient [8, 9]. Therefore administration of H_2 receptor blockers alone does not guarantee a safe gastric environment. However, two exciting observations emerged from these and related studies [10–12]. First, prolonged fluid deprivation was associated with increasing gastric volume and decreasing pH. Second, ingestion of fluid (water, coffee or juice) associated with either an increase in gastric volume (indeed, in some patients the volume decreased) or a significant change in pH (in some patients, pH increased). It would seem, therefore, that, far from protecting the patient, withholding fluid may be harmful in terms of both an adverse effect on the gastric environment and other indices of morbidity [13, 14], whereas administration is potentially beneficial.

Many investigators have examined the question of how long patients should fast. The basic method of study is outlined well by Phillips, Hutchinson and Davidson [1] in the present issue. Five, 4, 3 and now

2 h have been shown to be little different with respect to ingestion of modest quantities of fluid (usually 150–300 ml) in both adults and children undergoing elective operations [1, 15–19]. These findings are hardly surprising when one considers that the normally functioning stomach can dispose of much greater fluid loads than any studied so far with a half-life of about 10–20 min [20]. It is important to stress that the patients in the studies described here have been healthy and undergoing elective surgery, and those with gastrointestinal disease or taking drugs which affect intestinal function have been excluded. Fluid administered before premedication is tolerated well [1, 21], but the effects of opioids on delaying gastric emptying have precluded studies after premedication.

The question of administration of fluid to emergency patients remains unresolved. One could argue that, having decided that an operation cannot be postponed, and knowing that there is no method which can reliably empty the stomach, any factor which might reduce gastric volume or acidity or dilute solid material should be tried, as this could prevent either respiratory obstruction or Mendelson's syndrome, should pulmonary aspiration occur. In contrast, increasing the stomach content when trauma, drugs or illness have slowed emptying may invoke vomiting or regurgitation and thus lead to an increased risk of pulmonary aspiration. One would not advocate abandoning rapid sequence induction of general anaesthesia with cricoid pressure, awake tracheal intubation if indicated, or the use of non-particulate antacids or H_2 receptor blockers for emergency anaesthesia in patients "with a full stomach", but we should determine if prior oral fluid administration should be part of such patient preparation. In addition, what evidence is there that the prolonged fast inflicted routinely on these patients is beneficial? One can be sure that the investigation of these matters will not be straightforward. Ethics Committees agonized long and hard over many of the studies described in the investigation of elective patients and, to their shame, some journals refused publication of the early results on ethical grounds. Tackling the issue of emergency operations will require careful planning, but should be done in the further interest of patient wellbeing.

Returning to elective operations, which concern the vast majority of patients requiring an anaesthetic, it is clear that "nil by mouth after midnight" should be abandoned. In its place, there should be agreement by anaesthetists, surgeons and nurses on guidelines that both day-case and inpatients may take, if they wish, clear fluids by mouth up to 3 h before surgery. This allows for the vagaries of operating lists and should not lead to cancellation of procedures for patients who overstep the mark, merely some rescheduling. The way has been led by a Canadian teaching hospital which modified its guidelines in 1988 to recommend a 3-h fast period for elective surgical patients [22]. The new guidelines have been well received [J. R. Maltby—personal communication]. The fear of some anaesthetists that, if the absolute fasting rule were relaxed, patients could not be trusted to drink only clear fluids but would feel free to eat and drink anything they wished, has not been fulfilled. Patients do occasionally admit to having eaten a full meal. The frequency is no greater than before the change in guidelines and the patient's usual explanation is that no instructions were given; whether there are clerical errors or the patient has not read the instructions in these instances is uncertain. Such occasions are rare. Two follow-up studies of day-case and inpatients confirmed that there was no difference in gastric fluid volume or pH between those patients who were allowed to drink and those who fasted from midnight [23, 24]. Anaesthetic organizations within the United Kingdom should follow the Canadian example. We should not have to wait a further 110 years for change. "Those who do not learn from history will be forced to relive it" [George Santayana (1863–1952)].

L. Strunin
Editor of Educational Reviews

REFERENCES

1. Phillips S, Hutchinson S, Davidson T. Preoperative drinking does not affect gastric contents. *British Journal of Anaesthesia* 1993; **70**: 6–9.
2. Dunnet JM, Zorab JSM. Nil by mouth after midnight? *Anaesthesia* 1992; **47**: 638.
3. Mendelson CL. The aspiration of stomach contents into the lungs during obstetric anesthesia. *American Journal of Obstetrics and Gynecology* 1946; **52**: 191–205.
4. Coté CJ. NPO after midnight for children—A reappraisal. *Anesthesiology* 1990; **72**: 589–592.
5. Olsson GL, Hallen B, Hambraeus-Jonzon K. Aspiration during anaesthesia: A computer aided study of 185,358 anaesthetics. *Acta Anaesthesiologica Scandinavica* 1986; **30**: 84–92.
6. Coté CJ, Goudsouzian NG, Liu LMP, Dedrick DF, Szyfelbein SK. Assessment of risk factors related to the acid aspiration syndrome in pediatric patients—gastric pH and residual volume. *Anesthesiology* 1982; **56**: 70–72.
7. Manchikanti L, Colliver JA, Marrero TC, Roush JR. Assessment of age-related acid aspiration risk factors in pediatric, adult, and geriatric patients. *Anesthesia and Analgesia* 1985; **64**: 11–17.
8. Durrant JM, Strunin L. Comparative trial of ranitidine and cimetidine on gastric secretion in fasting patients at induction of anaesthesia. *Canadian Anaesthetists Society Journal* 1982; **29**: 446–451.
9. Sandhar BK, Goresky GV, Maltby JR, Shaffer EA. Effect of oral liquids and ranitidine on gastric fluid volume and pH in children undergoing outpatient surgery. *Anesthesiology* 1989; **71**: 327–330.
10. Hutchinson A, Maltby JR, Reid CRG. Gastric fluid volume and pH in elective patients. Part 1: Coffee or orange juice *versus* overnight fast. *Canadian Journal of Anaesthesia* 1988; **35**: 12–15.
11. Sutherland AD, Stock JG, Davies JM. Effects of preoperative fasting on morbidity and gastric contents in patients undergoing day stay surgery. *British Journal of Anaesthesia* 1986; **58**: 876–878.
12. Scarr M, Maltby JR, Jani K, Sutherland LR. Volume and acidity of residual gastric fluid after oral fluid ingestion before elective ambulatory surgery. *Canadian Medical Association Journal* 1989; **14**: 1114–1115.
13. Goodwin APL, Roe WL, Ogg TW. Oral fluids prior to day surgery. The effect of shortening the preoperative fluid fast on postoperative morbidity. *Anaesthesia* 1991; **46**: 1066–1068.
14. Cobley M, Dunne JA, Sanders LD. Stressful pre-operative preparation procedures. *Anaesthesia* 1991; **46**: 1019–1022.
15. Maltby JR, Sutherland AD, Sale JP, Shaffer EA. Preoperative oral fluids: is a five hour fast justified prior to elective surgery? *Anesthesia and Analgesia* 1986; **65**: 1112—1116.
16. Miller M, Wishart HY, Nimmo WS. Gastric contents at

induction of anaesthesia. Is a four hour fast necessary? *British Journal of Anaesthesia* 1983; **55**: 1185–1187.

17. Maltby JR, Lewis P, Martin A, Sutherland LR. Gastric fluid volume and pH in elective patients following unrestricted oral fluids until 3 hours before surgery. *Canadian Journal of Anaesthesia* 1991; **38**: 425–429.
18. Schreiner MS, Triebwasser A, Keon TP. Oral fluids compared to preoperative fasting in pediatric outpatients. *Anesthesiology* 1990; **72**: 593–597.
19. Splinter WM, Stewart JA, Muir JG. The effect of preoperative apple juice on gastric contents, thirst and hunger in children. *Canadian Journal of Anaesthesia* 1989; **36**: 55–58.
20. Hunt JN. Some properties of an alimentary osmoreceptor mechanism. *Journal of Physiology* (*London*) 1956; **132**: 267–288.
21. Maltby JR, Koehli N, Ewen A, Shaffer EA. Gastric fluid volume, pH and emptying in elective inpatients. Influences of narcotic–atropine premedication, oral fluid, and ranitidine. *Canadian Journal of Anaesthesia* 1988; **35**: 562–566.
22. The shortened fluid fast and the Canadian Anaesthetists Society new guide-lines for fasting in elective/surgical patients. *Canadian Journal of Anaesthesia* 1990; **37**: 905–906.
23. Scarr M, Maltby JR, Jani K, Sutherland LR. Volume and acidity of residual gastric fluid after oral fluid ingestion before elective ambulatory surgery. *Canadian Medical Association Journal* 1989; **14**: 1151–1154.
24. Maltby JR, Lewis P, Martin A, Sutherland LR. Gastric fluid volume and pH in elective patients following unrestricted oral fluid until 3 hours before surgery. *Canadian Journal of Anaesthesia* 1991; **38**: 425–429.

EDITORIAL II

POSTOPERATIVE ANALGESIA IN CHILDREN

The recurring challenge of postoperative pain control in children is examined again in a study published in this issue of the Journal [1]. There are well known difficulties in this area: for example, assessment of pain in preverbal and preschool children, measurement of its intensity in this age group and of the relief gained from therapeutic interventions [2]. Recording and assessment of postoperative pain relief are recommended by the *Report of the Joint College Working Party on Pain after Surgery* [3]. However, detailed consistent assessment can be made only if there are available trained staff who are familiar with the behavioural and subjective effects of pain in children, in a suitable environment [4].

Several techniques have been developed recently in an attempt to improve upon traditional i.m. administration of opioids in children. I.v. infusion of opioids has been advocated [5], but the technique has not achieved widespread favour, possibly because of reluctance to use a method which in adults had a reputation for producing respiratory depression and episodic desaturation, particularly during sleep [6–8]. In addition, many anaesthetists regard the use of i.v. infusion techniques as an indication for postoperative care in an intensive care unit (ICU) or high dependency unit (HDU), or a nurse to patient staffing ratio of 2:1 in a dedicated postoperative ward. Such facilities are not always available, but the absence of an HDU has been highlighted recently as a factor in perioperative morbidity [9] and this may act as an impetus for improvement.

Curiously, there are few reports of respiratory depression in children after i.v. opioid infusions. Wolf and Hughes found significantly decreased ventilatory frequencies and oxygen saturation in a group of children given i.v. opioids [1], but this was not clinically important and other investigators found that an infusion of papaveretum 23 $\mu g\ kg^{-1}\ h^{-1}$ in 29 infants aged up to 6 months resulted in only one episode of respiratory depression [10]. However, the number of patients exposed to this technique to date is small compared with the number of adults for whom data are available, so these studies should not be taken as an indication that the technique is safe.

Monitoring of ventilatory frequency has been shown to be an insensitive index of the likelihood of respiratory depression; pulse oximetry should also be used when i.v. infusions are used in the spontaneously breathing child [11]. Continuous monitoring and frequent observation are essential safety measures [10] and therefore the appropriate environment is likely to be one in which adequate staffing ratios and HDU facilities exist.

Patient controlled analgesia (PCA) has been used in children older than 6 yr in both the U.S.A. [12] and the U.K. [13]. However, there are many details of technique which require clarification before PCA becomes a generally accepted technique: for example, what is the best opioid?; may the activating device for a PCA devised for adults be modified appropriately for children with small hands?; what is the appropriate lockout time?; does a background infusion provide superior analgesia compared with a bolus-alone technique? In adults, the use of a background infusion has been shown by some workers to produce no improvement in analgesia [14] and its routine use has been questioned [15]. The answer to these questions on PCA in children will require carefully designed clinical studies and it is fortunate that the recently published Department of Health guidelines on local research Ethics Committees chose to modify the draft proposal that non-therapeutic research in children should be abandoned [16].

Regional analgesia provides excellent analgesia for a relatively short period of time and is particularly appropriate in orthopaedic and lower abdominal surgery for control of postoperative pain [17]. Wolf and Hughes noted similar degrees of analgesia in a comparison of extradural bupivacaine by infusion with i.v. morphine [1]. However, regional anaesthetic techniques do possess some disadvantages: in the case of caudal extradural blocks, urinary retention has been reported in up to 65% of patients [18] and persistent motor block may occur in up to 30% [19]. More extensive blocks may result in total absence of sensation over large areas and this may be confusing to children and lead to restlessness. This side effect was noted in up to 19% of children given extradural bupivacaine [1]. Wolf and Hughes have suggested that i.v. morphine may be preferable as a sole analgesic or adjuvant in children who are likely to be overactive after surgery [1]. When some type of sedation is added to a local anaesthetic regimen in young children, particular care should be exercised to restrict the dosage of opioid as the balance of pain and respiratory depression may be disturbed [20].

It is stated frequently that one of the major reasons for avoiding i.m. administration of opioids in children is the associated pain of injection. However, attempts to avoid i.m. injections in children have resulted in a fatal outcome as a result of an inappropriate alternative prescription using the rectal route of administration [21]. Subcutaneous insertion of a cannula represents one method of obviating repeated i.m. injections. A cannula is placed at the time of anaesthesia, covered with a sterile dressing and flushed with heparinized saline in the postoperative period [22]. The cannula may be used for administration of s.c. morphine on an as-required basis as the sole method of providing analgesia or in reduced dosage to supplement regional anaesthetic techniques.

A phenomenon of late postoperative pain has been described with which postoperative pain worsens between 12 and 24 h after anaesthesia, either as a result of regression of a local anaesthetic block or possibly by elimination of drugs given during anaesthesia or for premedication. Drugs without respiratory depressant effects may be used to overcome this problem, for example regular administration of a non-steroidal analgesic drug (NSAID) with morphine. Ibuprofen has a short half-life but regular 8-hourly rectal administration was shown to reduce morphine requirements by 19% after abdominal hysterectomy [23] and rectal diclofenac has been shown to provide good analgesia in children after discharge from hospital after minor surgery [24]. The rectal route avoids painful i.m. injections with diclofenac, but unfortunately the suppositories of this drug are available in strengths of 12.5 mg and 100 mg, whereas many children require a dose intermediate between these two. Another method of extending analgesia is to combine opioids with local anaesthetic drugs in an extradural bolus or infusion technique [25]. This technique has been used in children and shown to be effective [26], although it was suggested that postoperative nursing of patients given combined local and opioid extradural infusions should take place in an HDU or extended recovery ward [27].

There have been several advances in recent years in the management of postoperative pain in adults. It is now evident that the problem of postoperative pain in children has also become an important issue. Whilst many techniques such as PCA may be used in older children, and it is gratifying to see the introduction of such regimens, there is still considerable scope for advances in pain therapy in infants and younger children.

D. Fell
Assistant Editor

REFERENCES

1. Wolf AR, Hughes D. Pain relief for infants undergoing abdominal surgery: a comparison of infusions of i.v. morphine and extradural bupivacaine. *British Journal of Anaesthesia* 1993; **70**: 10–16.
2. Lloyd-Thomas AR. Pain management in paediatric patients. *British Journal of Anaesthesia* 1990; **64**: 85–104.
3. The Royal College of Surgeons of England & College of Anaesthetists. Commission on the Provision of Surgical Services. *Report of the Working Party on Pain after Surgery.* London: HMSO, 1990.
4. Lloyd-Thomas AR, Howard R. Postoperative pain control in children. *British Medical Journal* 1992; **304**: 1174–1175.
5. Bray RJ. Postoperative analgesia provided by morphine infusion in children. *Anaesthesia* 1983; **38**: 1075–1078.
6. Catling JA, Pinto DM, Jordan C, Jones JG. Respiratory effects of analgesia after cholecystectomy: comparison of continuous and intermittent papaveretum. *British Medical Journal* 1980; **281**: 478–480.
7. Catley DM, Thornton C, Jordan C, Lehane JR, Royston D, Jones JG. Pronounced episodic oxygen desaturation in the postoperative period: Its association with ventilatory pattern and analgesic regimen. *Anesthesiology* 1985; **63**: 20–28.
8. Ray DC, Drummond GB. Continuous intravenous morphine for pain relief after abdominal surgery. *Annals of the Royal College of Surgeons of England* 1988; **70**: 317–321.
9. Campling EA, Devlin HB, Hoile RW, Lunn JN. National Confidential Enquiry into Perioperative Deaths. *The Report of the National Confidential Enquiry into Perioperative Deaths 1990.* London: HMSO, 1992.
10. Jones SEF, Stokes MA. Papaveretum infusions in children under 6 months of age. *Anaesthesia* 1992; **46**: 688–690.
11. Wheatley RG, Somerville ID, Sapsford DJ, Jones JG. Postoperative hypoxaemia: Comparison of extradural i.m. and patient-controlled opioid analgesia. *British Journal of Anaesthesia* 1990; **64**: 267–275.
12. Berde CB, Lehn BM, Yee JD, Sethna NF, Russo D. Patient-controlled analgesia in children and adolescents: A randomized prospective comparison with intramuscular administration of morphine for postoperative analgesia. *Journal of Pediatrics* 1991; **118**: 460–466.
13. Lawrie SC, Forbe DW, Akhtar TM, Morton NS. Patient-controlled analgesia in children. *Anaesthesia* 1990; **45**: 1074–1076.
14. Owen H, Szekely SM, Plummer JL, Cushnie JM, Mather LE. Variables of patient-controlled analgesia 2. Concurrent infusion. *Anaesthesia* 1989; **44**: 11–13.
15. White PF, Parker RK. Is the risk of using a "basal" infusion with patient-controlled analgesia therapy justified? *Anesthesiology* 1992; **76**: 489.
16. Moodie PCE, Marshall T. Guidelines for local research ethics committees. *British Medical Journal* 1992; **304**: 1293–1295.
17. Arthur DS, McNicol LR. Local anaesthetic techniques in paediatric surgery. *British Journal of Anaesthesia* 1986; **58**: 760–778.
18. Vater M, Wandless JG. Caudal or dorsal nerve block? A comparison of two local anaesthetic techniques for postoperative analgesia following day case circumcision. *Acta Anaesthesiologica Scandinavica* 1985; **29**: 175–179.
19. Yeoman PM, Cooke R, Hain WR. Penile block for circumcisions? A comparison with caudal blockade. *Anaesthesia* 1983; **38**: 862–866.
20. McQuay HJ. Potential problems of using both opioids and local anaesthetic. *British Journal of Anaesthesia* 1988; **61**: 121.
21. Gourlay GK, Boas RA. Fatal outcome with use of rectal morphine for postoperative pain control in an infant. *British Medical Journal* 1992; **304**: 766–767.
22. Lavies NG, Wandless JG. Subcutaneous morphine in children: taking the sting out of postoperative analgesia. *Anaesthesia* 1989; **44**: 1000–1001.
23. Owen H, Glavin RJ, Shaw NA. Ibuprofen in the management of postoperative pain. *British Journal of Anaesthesia* 1986; **58**: 1371–1375.
24. Moores MA, Wandless JG, Fell D. Paediatric postoperative analgesia: A comparison of rectal diclofenac with caudal bupivacaine after inguinal herniotomy. *Anaesthesia* 1990; **45**: 156–158.
25. Akerman B, Arwestrom E, Post C. Local anesthetics potentiate spinal morphine antinociception. *Anesthesia and Analgesia* 1988; **67**: 943–948.
26. Wolf AR, Hughes D, Wade A, Mather SJ, Prys-Roberts C. Postoperative analgesia after paediatric orchidopexy: Evaluation of a bupivacaine–morphine mixture. *British Journal of Anaesthesia* 1990; **64**: 430–435.
27. Striebel HW, Gottschalk B. Caudal bupivacaine in children: where should they be nursed? *Anaesthesia* 1991; **46**: 899–890.

British Journal of Anaesthesia 1993; 70: 6–9

ORIGINAL ARTICLES

PREOPERATIVE DRINKING DOES NOT AFFECT GASTRIC CONTENTS

S. PHILLIPS, S. HUTCHINSON AND T. DAVIDSON

SUMMARY

We have compared the effect of allowing free clear fluids until the time of oral premedication with conventional preoperative fasting. In a prospective, randomized trial, the residual volume and pH of gastric contents after induction of anaesthesia were measured in 100 elective surgical patients allocated randomly to a group in whom the intake of free clear fluids up to the time of premedication was measured (mean 388 ml in 6 h before surgery) or a control group who were fasted for 6 h. Preoperative drinking did not affect either mean (SD) residual gastric volume (22 (21) ml in the study group vs *19 (16) ml in the control group) or pH (study group 2.64 (1.57)* vs *control group 2.26 (1.45)). The study group experienced less preoperative thirst. Problems with aspiration or regurgitation were not encountered. We believe that allowing elective surgical patients to drink clear fluids until 2 h before anaesthesia may enhance patient comfort without compromising safety.* (Br. J. Anaesth. 1993; **70**: 6–9)

KEY WORDS

Gastrointestinal tract: fasting, gastric volume, preoperative fluid intake.

It is accepted widely that the risk of Mendelson's syndrome is reduced by minimizing the volume and increasing the pH of the gastric contents. To minimize the residual gastric volume (RGV), patients have been fasted traditionally for 4–6 h before surgery. This fasting interval is standard practice [1–3], but is not in keeping with the physiology of gastric emptying. A light meal leaves the stomach in 1.5–3 h and clear fluids almost immediately [1, 4]. Thus the conventional fast may be over-cautious, and reducing the fasting time may not increase the risk of pulmonary aspiration.

The preoperative fast is unpleasant for patients, who complain frequently of thirst and dry mouth. This is especially so in hot weather, when antisialagogue premedication has been prescribed and when theatre delays and cancellations occur. The ensuing dehydration may make anaesthesia more hazardous and contributes to perioperative morbidity [5–7].

Several workers have questioned the need for the conventional preoperative fasting period [8, 9]. In children, allowing clear fluid ingestion up to 2 h before surgery does not affect the volume or pH of gastric contents [10–12]. In adolescents, unlimited fluid ingestion until 3 h before surgery decreased thirst and did not affect gastric contents [13]. In adult practice, the same findings have not been documented in any controlled study. The incidence of aspiration pneumonitis is low [14] and appears to be unrelated to the gastric volume [15]. The ingestion of 150 ml of orange juice or coffee, 2–3 h before operation [16], or of 150 ml of tea, coffee or apple juice 3 h before operation in patients undergoing day-case surgery [17] did not increase the risk of aspiration pneumonitis; unrestricted oral fluids until 3 h before surgery also had no effect in a retrospectively controlled trial [18].

Our study was designed to assess if allowing unrestricted clear fluids until 2 h before anaesthesia would alter the gastric volume and pH, affect anaesthetic complications such as regurgitation or aspiration, and enhance patient comfort.

PATIENTS AND METHODS

The study was a prospective, randomized controlled trial. The investigation was approved by the local Ethics Committee and each patient gave written informed consent.

One hundred patients (ASA grades I–III, > 18 yr) undergoing elective surgery were studied. Patients were excluded if factors known to affect the gastric contents were present—pregnancy, gastrointestinal disease and the ingestion of alcohol, opioids, anticholinergics, histamine type-2 receptor antagonists or metoclopramide in the 24 h before surgery. Patients were allocated randomly, on alternate weeks, to either the control or the study group and received either no premedication or temazepam 10–20 mg with water 30 ml 2 h before operation, at the discretion of the anaesthetist in charge of the case.

This article is accompanied by Editorial I.

Stephanie Phillips*, B.Med., F.R.C.Anaes., Susan Hutchinson, M.B., B.S., F.R.C.Anaes. (Department of Anaesthetics); Timothy Davidson, Ch.M., M.R.C.P., F.R.C.S. (Department of Surgery); Kingston Hospital, Kingston-upon-Thames, Surrey KT2 7QB.
Accepted for Publication: June 23, 1992.

*Present address, for correspondence: Department of Anaesthetics, St George's Hospital, Blackshaw Road, London SW17.

TABLE I. *Patient characteristics (number, or mean (range or SD))*

	Study group ($n = 50$)	Control group ($n = 50$)
Age (yr)	64 (21–88)	55 (20–86)
Sex (M:F)	34:16	40:10
Height (cm)	169 (11)	169 (10)
Weight (kg)	72 (15)	73 (14)
ASA (I:II:III)	18:30:2	29:19:2
Operation (major:intermediate)	18:32	23:27
Premedication	35	22

TABLE II. *Fasting duration and volume of fluid ingested in 6 h before surgery (mean (SD))*

	Study group	Control group
Solids fast (h)	14.8 (8.9)	14.6 (8.9)
Fluid fast (h)	2.2 (0.7)	12.9 (9.0)
Fluid intake (ml)	388 (238)	13 (15)

Patients in the control group were fasted from midnight for a morning list and from 06:30 for an afternoon list. Patients in the study group were allowed unrestricted clear fluids (alcoholic drinks and those containing milk or sugar were not allowed), until 2 h before surgery was expected to begin, a time marked by the administration of the premedication if prescribed. The volume of fluid consumed and the time at which the "nil by mouth" order was implemented were recorded on the ward fluid balance chart by the nursing staff. No changes were made to theatre schedules in order to accommodate the varying fasting intervals.

The following data were recorded for each patient: age, sex, height, weight, ASA grade, smoking habit, fasting duration, volume of fluid ingested in the 6 h before surgery and the occurrence of complications possibly attributable to recent ingestion of fluid. Patients were asked to grade the degree of thirst and hunger as nil, mild, moderate or severe immediately before induction of anaesthesia.

Anaesthesia was administered according to the surgical requirements and the preference of the anaesthetist in charge of the case. Immediately after induction, an 18-French gauge Salem sump tube (Argyle) was passed orally into the stomach and correct positioning confirmed either by aspiration of gastric contents or, if none was obtained, by auscultation of 2 ml of insufflated air. Aspiration was performed by an assistant who was unaware of the duration of the patient's fluid fast. All aspiration was performed with the patient supine, in three different tube positions with the stomach being massaged to assist complete emptying. The volume of fluid and pH were measured as soon as possible after collection. The pH was measured with a radiometer (Corning 150), calibrated to two points, 4.0 and 7.0.

Throughout the study, comparison of the groups was made after every 10 patients, to ensure that the study group was not at an increased risk of Mendelson's syndrome.

RGV and pH were compared using the two-sample Student's t test. Proportions were compared using the standard error of the difference between two proportions method. Results are presented as confidence intervals for the difference, with probability levels. Thirst and hunger were compared using the chi-square test.

RESULTS

Patient characteristics were similar in both groups (table I). The groups were comparable also with respect to ASA grade, smoking history and surgical procedure. Major procedures included cholecystectomy, transurethral resection of the prostate and bowel resection. Intermediate procedures included varicose vein surgery, inguinal hernia repair and cystodiathermy. Premedication was prescribed more often in the study group.

No patient was permitted solid food for 6 h before operation; in both groups, the duration of this fast was usually considerably longer (table II). As expected, the duration of the nil-by-mouth period varied less in the study group (1–4 h) than in the control group (6–23 h).

In the study group, the fluid intake in the 6 h before surgery ranged from 50 to 1200 ml. Fluid was ingested by the control group for the purposes of taking oral premedication only. RGV and pH were similar in both groups (table III). The number of patients considered to be at risk of Mendelson's syndrome (those with RGV greater than 0.4 ml kg^{-1} with pH less than 2.5 [19]) was the same in both groups.

Ingested fluid volume did not correlate with RGV or pH. The gastric pH of patients drinking until 2 h before operation was greater than in those who had fasted, but this was not statistically significant.

Patients in the study group experienced less thirst than those in the control group (table IV).

No patient regurgitated or aspirated.

DISCUSSION

Our study has shown that allowing elective surgical patients to drink until 2 h before surgery decreases thirst without prejudicing safety. The ingestion of

TABLE III. *Residual gastric volume (RGV) and pH (mean (range)). CI = Confidence interval for difference*

	Study group	Control group	CI	*P*
RGV (ml)	21 (0–80)	19 (0–63)	−5 to +9	0.58
pH	2.64 (1.07–6.82)	2.26 (1.25–7.03)	−2.5 to +0.8	0.07
Percent of patients with				
RGV > 0.4 ml kg^{-1}	26	22	−13 to +21	0.64
pH < 2.5	76	87	−24 to +6	0.25
Both	20	20	−16 to +17	0.96

TABLE IV. *Thirst and hunger*

	Thirst		Hunger	
	Study group	Control group	Study group	Control group
Nil	34	7	23	12
Mild	13	9	9	11
Moderate	2	11	11	12
Severe	2	23	7	15
	$P < 0.001$		$P = 0.09$	

free clear fluids until the time of oral premedication does not affect either the volume or pH of gastric contents. If the risk of regurgitation is related to the RGV, it is unaltered by preoperative drinking. Should regurgitation occur, patients who have been drinking are at no greater risk of Mendelson's syndrome than those who have fasted. The gastric pH in the study group tended to be greater, and greater than 2.5 more often, than in the control group, although this difference was not significant. This finding may reflect the dilution of gastric acid by the ingested fluids.

In practice, the period of preoperative fast is often prolonged and the mean fasting period of around 13 h in our control group is not atypical. Indeed, the inevitable constraints of conventional fasting, together with alterations in theatre schedules imply that there is a wide variability in the fasting period. Patients find the ensuing hunger and thirst unpleasant, and if antisialagogue premedication had been used this may be even more pronounced than in our control group. In the study group, thirst was a less common and less severe complaint.

Measurement of gastric volume using an aspiration technique may be criticized as underestimating the RGV, but when a multi-orifice sump tube is used the method has been shown to be valid [20]. In any event, any sampling error should be small and consistent between groups.

Temazepam has no effect on gastric emptying or pH [21]. Temazepam was prescribed more often in the study group than in the control group. It is possible that control group patients may have been more anxious, resulting in delayed gastric emptying compared with study group patients. Nevertheless, the RGV was the same in both groups.

We excluded patients with factors likely to delay gastric emptying, such as pregnancy, trauma, opioid administration, and when mechanical or neurological factors such as pyloric stenosis, vagotomy or autonomic neuropathy existed. Our findings cannot be extrapolated to such patients.

Further studies are needed to evaluate the effect of preoperative drinking in patients prescribed opioid–anticholingeric premedication. Similarly, the relevance of our findings in day-case patients should be investigated. Nausea and vomiting are known to be related to the duration of the preoperative fasting period [6]. These aspects were not examined in our study, but investigation of the effect of preoperative drinking on patient recovery is warranted.

In the U.K., patients are scheduled to fast for 4–6 h before induction of anaesthesia, although recent guidelines from the Canadian Anaesthetists' Society have reduced the fluid fast period to 3 h [22]. Our findings support this shorter fluid fast on the basis that patient comfort is increased and safety is not compromised.

ACKNOWLEDGEMENTS

We thank Dr M. Bland, Senior Lecturer in Medical Statistics, St George's Hospital Medical School and Mr D. Simms, Top-Grade Biochemist, Kingston Hospital for the gastric pH estimations.

REFERENCES

1. Gregory IC. Anaesthesia and the gastrointestinal tract. In: *Wylie and Churchill Davidson's A Practice of Anaesthesia*, 5th Edn. London: Lloyd Luke, 1984; 940–942.
2. Atkinson RS, Rushman GB, Lee JA (eds). *A Synopsis of Anaesthesia*, 10th Edn. Bristol: Wright, 1987; 112.
3. Aitkenhead AR, Smith G (eds). *Textbook of Anaesthesia*, 2nd Edn. London, Edinburgh: Churchill Livingstone, 1990; 341.
4. Beaumont W. *Gastric Juice and the Physiology of Digestion.* Blattsburgh: Allen, 1833; 159–160, 277.
5. Sutherland T, Davies JM, Stock J. The price of preoperative outpatient fasting—effects on gastric contents and outpatient morbidity. *Canadian Anaesthetists Society Journal* 1985; **32**: S100.
6. Sutherland AD, Stock JG, Davies JM. Effects of preoperative fasting on morbidity and gastric contents in patients undergoing day-stay surgery. *British Journal of Anaesthesia* 1986; **58**: 876–878.
7. Goodwin APL, Rowe WL, Ogg TW, Samaan A. Oral fluids prior to day surgery—the effect of shortening the preoperative fluid fast on postoperative morbidity. *Anaesthesia* 1991; **46**: 1066–1068.
8. Maltby JR, Sutherland AD, Sale JP, Shaffer EA. Preoperative oral fluids: is a five-hour fast justified prior to elective surgery? *Anesthesia and Analgesia* 1986; **65**: 1112–1116.
9. Miller M, Wishart HY, Nimmo WS. Gastric contents at induction of anaesthesia. Is a four-hour fast necessary? *British Journal of Anaesthesia* 1983; **55**: 1185–1187.
10. Crawford M, Lerman J, Christensen S, Farrow-Gillespie A. Effects of duration of fasting on gastric fluid pH and volume in healthy children. *Anesthesia and Analgesia* 1990; **71**: 400–403.
11. Splinter WM, Schafer JD. Unlimited clear fluid ingestion two hours before surgery in children does not affect volume or pH of stomach contents. *Anaesthesia and Intensive Care* 1990; **18**: 522–526.
12. Schreiner MS, Triebwasser A, Keon TP. Ingestion of liquids compared with preoperative fasting in pediatric outpatients. *Anesthesiology* 1990; **74**: 593–597.
13. Splinter WM, Schafer JD. Ingestion of clear fluids is safe for adolescents up to three hours before anaesthesia. *British Journal of Anaesthesia* 1991; **66**: 48–52.
14. Olsson GL, Hallén B, Hamraes-Jonzon K. Aspiration during anaesthesia: a computer aided study of 185,358 anaesthetics. *Acta Anaesthesiologica Scandinavica* 1986; **30**: 84–92.
15. Hardy JF, Lepage Y, Bonneville-Chouinard N. Occurrence of gastroesophageal reflux on induction of anaesthesia does not correlate with the volume of gastric contents. *Canadian Journal of Anaesthesia* 1990; **37**: 502–508.
16. Hutchinson A, Maltby JR, Reid CRG. Gastric fluid and pH in elective patients. Part I: Coffee or orange juice versus overnight fast. *Canadian Journal of Anaesthesia* 1988; **35**: 12–15.
17. Scarr M, Maltby JR, Jani K, Sutherland LR. Volume and acidity of residual gastric fluid after oral ingestion before elective ambulatory surgery. *Canadian Medical Association Journal* 1989; **141**: 1151–1154.
18. Maltby JR, Lewis P, Martin A, Sutherland LR. Gastric fluid volume and pH in elective patients following unrestricted oral fluid until 3 hours before surgery. *Canadian Journal of Anaesthesia* 1991; **38**: 425–429.

19. Roberts RB, Shirley MA. Reducing the risk of acid aspiration syndrome during Caesarean section. *Anesthesia and Analgesia* 1974; **53**: 859.
20. Hardy JF, Plourde G, Lebrun M, Coté C, Dube S, Lepage Y. Determining gastric contents during general anaesthesia: evaluation of two methods. *Canadian Journal of Anaesthesia* 1987; **34**: 474–477.
21. Goodman LS, Gilman A, eds. *Goodman and Gilman's The Pharmacological Basis of Therapeutics*, 6th Edn. London: Macmillan, 1980; 346.
22. The shortened fluid fast and the Canadian Anaesthetist's Society's new guide-lines for fasting in elective/emergency patients. *Canadian Journal of Anaesthesia* 1990; **37**: 905–906.

British Journal of Anaesthesia 1993; 70: 10–16

PAIN RELIEF FOR INFANTS UNDERGOING ABDOMINAL SURGERY: COMPARISON OF INFUSIONS OF I.V. MORPHINE AND EXTRADURAL BUPIVACAINE

A. R. WOLF AND D. HUGHES

SUMMARY

We have undertaken a prospective, randomized double-blind study to compare extradural bupivacaine infusions with i.v. morphine infusions for postoperative analgesia in 32 infants younger than 4 yr undergoing abdominal surgery. "Sham" extradural or i.v. catheters were used to maintain the blinded nature of the study. Both techniques provided adequate analgesia for most of the 36-h postoperative period; differences in the pattern or quality of the analgesia were not detected. Patients in the i.v. morphine group were significantly more sedated; this was accompanied by slower ventilatory frequencies (26.7 (SD 1.8) b.p.m.) compared with the extradural group (33.6 (1.3) b.p.m.). Similarly, oxygen saturation was significantly less ($P < 0.01$) in patients receiving morphine (medians and quartiles of 94.0 (93–96)% compared with 96.0 (93–96)%). Mean systolic arterial pressure was similar in the two groups and there were no life-threatening complications. The lack of sedation was troublesome in three patients in the extradural group. (Br. J. Anaesth. 1993; **70**: 10–16)

KEY WORDS

Anaesthetics local, bupivacaine. Analgesia: postoperative, paediatric. Analgesics: morphine infusion. Anaesthetic techniques: extradural infusion.

The current debate on management of pain in neonates [1] has encouraged renewed interest in the use of regional analgesia for infants undergoing surgery. Extradural anaesthesia with bupivacaine has been shown to modify the haemodynamic [2], hormonal [3] and metabolic [4] responses to surgery in children, and provides effective postoperative analgesia [5]. However, insertion of a lumbar or thoracic extradural block in a small infant requires a high level of technical expertise, and identification of the extradural space becomes progressively more difficult with decreasing age of the subject [2]. A technique of inserting an extradural catheter up to a thoracic level via the easier caudal route has been used in neonates and infants to provide local anaesthesia during upper abdominal surgery [6]. A similar technique with extradural morphine has been described for postoperative analgesia [7].

Variable rate i.v. opioid infusions are used even in young infants for postoperative analgesia, but may have serious side effects such as impaired consciousness or ventilatory depression [8]. Extradural infusions of bupivacaine offer an alternative which avoids opioids, but also has the potential to produce hypotension and complications from extensive local block [9] or systemic absorption of local anaesthetic [10]. We are not aware of any study in this age group comparing analgesia, recovery and side effects of these two techniques. We therefore designed a randomized double-blinded study to evaluate the use of i.v. morphine infusions and extradural infusions of bupivacaine after abdominal surgery in infants and small children.

PATIENTS AND METHODS

After obtaining approval by the local Ethics Committee and informed parental consent, we studied 32 healthy patients (ASA status I and II) aged less than 4 yr undergoing elective abdominal, renal or bladder surgery. Infants older than 4 months received oral trimeprazine 1.5 mg kg^{-1} and topical EMLA (eutectic mixture of local anaesthetic) 90 min before the estimated time of surgery, while those younger than 4 months were not premedicated. Thiopentone and alcuronium were given i.v. at induction of anaesthesia. After tracheal intubation, the lungs were ventilated to normocapnia with 70% nitrous oxide and enflurane up to 1% in oxygen. During operation, an infusion of 5% glucose and 0.225% sodium chloride was given for fluid maintenance, and other fluid losses were replaced with Hartmann's solution, blood or blood products. In addition to this standardized general anaesthetic, patients were allocated randomly to receive either i.v. morphine or extradural bupivacaine during and after surgery. The 16 patients assigned to the i.v. morphine group had a second i.v. cannula inserted before the start of surgery, specifically for the morphine infusion. After a loading dose of morphine 0.15 mg kg^{-1}, an infusion of morphine in 50 ml of 0.9% saline was started. Solutions were made at different concentrations to take into account the increased sensitivity of younger

---

This article is accompanied by Editorial II.

A. R. Wolf*, M.A., M.B., B.CHIR., F.R.C.ANAES.; D. Hughes, M.D., M.B., CH.B., F.R.C.ANAES.; Sir Humphry Davy Department of Anaesthesia, University of Bristol, Bristol Royal Hospital for Sick Children, Bristol BS2 8HW. Accepted for Publication: July 30, 1992.

*Present address, for correspondence: Department of Anaesthesia, Royal Hospital for Sick Children, Yorkhill, Glasgow G3 8SJ.

children to opioids: a 50-μg ml^{-1} solution for children weighing less than 10 kg and a 100-μg ml^{-1} solution for those heavier than 10 kg. Initial infusion rates were 0.1 ml kg^{-1} h^{-1} (5 μg kg^{-1} h^{-1} for < 10 kg and 10 μg kg^{-1} h^{-1} for > 10 kg) and corresponded to the usual starting dosage for morphine infusions in infants at the Bristol Royal Hospital for Sick Children. The 16 patients allocated to the extradural group were turned on their left side before starting surgery, and under sterile conditions an 18- or 19-gauge Tuohy needle from a Portex minipack system 1 (Ref: 100/391/118 or 100/391/019) was inserted through the sacrococcygeal hiatus. After the absence of blood or CSF was confirmed, the catheter (0.9 mm or 0.63 mm o.d.) was inserted rostrally to a distance calculated to leave the tip between the first and second lumbar vertebrae. An initial dose of 0.25% plain bupivacaine was injected according to the formula by Takasaki [11] relating the volumes of injectate to the required number of spinal segments to be blocked (0.05 ml kg^{-1} per segment). An infusion of 0.25% bupivacaine was commenced immediately after the initial dose and infused throughout surgery at a rate of 0.1 ml kg^{-1} h^{-1}. Intraoperative heart rate and arterial pressure were measured at 5-min intervals and were maintained within 20% of the preoperative values using additional doses of either morphine 40 μg kg^{-1} or 0.25% bupivacaine up to a maximum of 1 ml kg^{-1}, depending on the group.

After surgery, patients were taken to a recovery area where the route of analgesia was disguised to prevent observer bias on pain observations. The analgesic solution (containing either morphine or bupivacaine) passed from the syringe pump labelled with the trial number to a bacterial filter wrapped in gauze and strapped to the chest. Two tubes emerged from the gauze wrapping. In the morphine group, the bacterial filter was connected to the i.v. cannula via covered infusion tubing, while a "sham" extradural cannula was strapped down the back to make it indistinguishable from a true extradural. In the extradural group, the bacterial filter was connected to the extradural cannula, while a sham i.v. infusion catheter and cannula were strapped to the arm under opaque tape to make them indistinguishable, by direct observation, from an i.v. cannula. Additional doses of i.v. morphine or extradural bupivacaine were given as necessary by one of the investigators to ensure that all patients were free from pain before returning to the ward and commencing pain observations.

On arrival of the patient in the ward, arterial pressure, oxygen saturation and ventilatory frequency were recorded. Sedation and analgesia were assessed after 1 h by a trained nurse observer who was unaware of the type of analgesia given. Further assessments were made hourly for the first 6 h, then 3-hourly up to 30 h and finally at 36 h according to observed behaviour during the preceding period. Sedation was assessed with a four-point scale: 0 = appropriately asleep; 1 = awake and alert; 2 = drowsy but responds to stimulation; 3 = very sedated. Pain measurement was based on a scoring system described by Hannallah and colleagues [12], which obtains a summed value of between 0 and 10 from observations of arterial pressure, crying, movement, agitation and localization of pain. If pain scores increased to greater than 4, the nursing staff were permitted to increase the infusion rate incrementally by 1 ml h^{-1} after informing one of the investigators. The maximum infusion rate permitted was 4 ml h^{-1}. The nurse observers were instructed to decrease the infusion rate and inform one of the investigators if systolic arterial pressure decreased to less than 20% of the baseline value, if ventilatory frequency decreased to less than 15 b.p.m. or if the patient became sedated or difficult to rouse (sedation score 3). Infusion rates could also be reduced incrementally according to usual ward practice if patients appeared to have little or no pain. Other recordings included major side effects or complications and the time to first bowel action after surgery. Oxygen saturation was monitored continuously during the infusions and set to alarm at oxygen saturations less than 85%. If parenteral analgesia was still required after 36 h, the patient continued with the same method of pain relief but in an unblinded fashion. Paracetamol was not prescribed routinely in the first 36 h, but could be given if the patient became pyrexial. While the nurse observers remained "blinded", it was necessary for the anaesthetic team to be aware of which infusion was being used. Any procedure that could result in unblinding the trial was carried out by another member of the ward staff or an anaesthetist. This included daily inspections of the i.v. and extradural sites to ensure that they remained clean and were functioning normally, but every effort was made to limit the interaction between the anaesthesia team and the nurse observers.

Statistical significance for parametric data was determined using analysis of variance and Student's *t* test. Ordinal data and nominal data were analysed by the Mann–Whitney *U* test and chi-square analysis with Yates' correction.

RESULTS

The ages, weights and duration of the surgical procedure did not differ significantly between the groups (table I).

Pain scores were categorized into three groups

TABLE I. *Patient data and duration of surgery (median (range)), with operation type by group allocation*

	Extradural group	Morphine group
Age (months)	9 (3–46)	14 (3–42)
Weight (kg)	9.8 (6.0–16.0)	11 (5.2–21.4)
Duration of op. (min)	125 (100–210)	120 (80–340)
Operation		
Reimplantation of ureters	7	3
Nephrectomy	5	4
Partial nephrectomy	1	2
Bladder surgery	1	1
Pyeloplasty	1	3
Pyelolithotomy	—	2
Laparotomy	1	—
Body wall sarcoma	—	1
Total	16	16

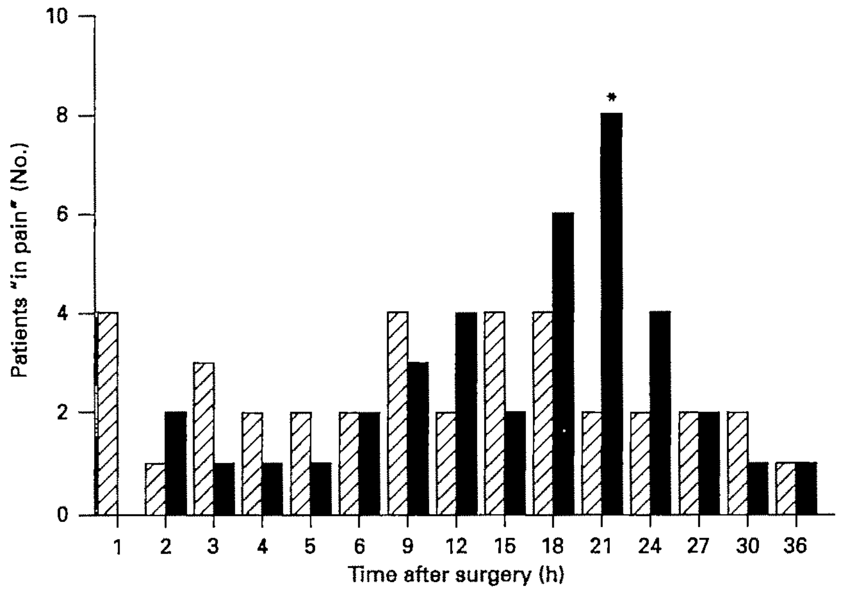


FIG. 1. Comparison of the numbers of patients in the extradural bupivacaine (▨) and morphine (■) groups with pain scores of 4 or more ("in pain") over the 36-h study period. *$P < 0.05$.

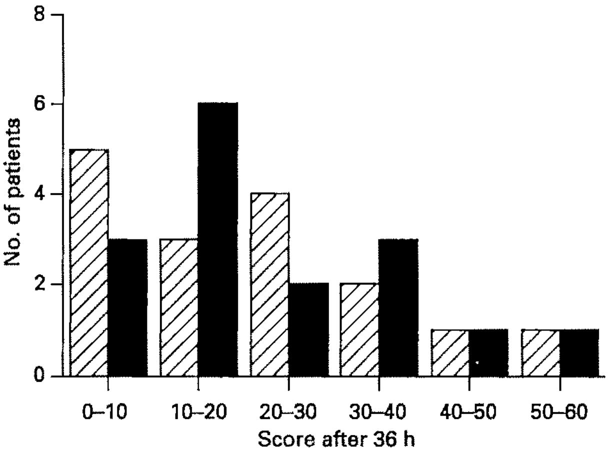


FIG. 2. Distribution of the total pain scores accumulated over 36 h (cumulative pain score) by each patient for the extradural bupivacaine (▨) and morphine (■) groups. Cumulative pain scores are displayed in bins of 10 on the X axis and the number of patients in each bin are shown on the Y axis.

according to previous experience with this scoring system: 0–3 = minimal or no pain; 4–6 = mild pain; 6 or greater = moderate to severe pain. The majority of patients were in the "no pain" category during the study, regardless of the designated method of analgesia. Comparison of the numbers of patients judged to have pain (pain score greater than 3) did not show any significant differences between the groups except at the 21-h observation (fig. 1). All patients completed the study and none had to be withdrawn because of failure of analgesia. There was variation in the quality of analgesia between patients which was reflected in the range of cumulative pain scores for each patient (fig. 2), but there was no difference in the distribution of cumulative pain scores between the groups.

Most patients required increases in the infusion rates from the baseline settings: extradural infusion rates varied from 0.1 to 0.4 ml kg^{-1} h^{-1}, while morphine delivery varied from 10 to 40 μg kg^{-1} h^{-1}. In both groups, the mean infusion rates increased to a maximum at 15 h and then declined. Increasing the infusion rates for those patients in pain appeared to control analgesia, although pain scores did not always decrease in the first 1 h after the increase. Further stepwise increases in infusion rate were often needed before pain was controlled. No patient required reduction of infusion rates because of hypotension or ventilatory depression. One patient in the extradural group was inadvertently given paracetamol for pain, and another three patients in each group were given paracetamol during the study because of pyrexia.

Patients in the bupivacaine group were less sedated than those in the morphine group (fig. 3).

Significant differences were observed during the first 1 h after operation and again at 27 and 30 h. The lack of sedation became troublesome in three of the patients having extradural infusions. The nurse observers noted agitation, fidgeting and restlessness as side effects in these patients. Although these patients could be settled without changing infusion rates, they needed regular attention to stop them from interfering with dressings and drains. It had been expected that sedation might interact with observed pain scores such that sedated patients would have lower pain scores than unsedated ones. However, while patients who were appropriately asleep (sedation 0) usually had a pain score of 3 or less for that observation period (96.6% in the extradural group and 98.2% in the morphine group), overall comparison of sedation scores and pain scores did not show a correlation in either of the groups.

Observed ventilatory frequencies were significantly less in the morphine group (fig. 4), and this was reflected in reduced oxygen saturation in the early postoperative period (fig. 5). Mean ventilatory frequencies over the 36-h study, calculated from an averaged value for each individual, were 33.6 (SD 1.3) b.p.m. in the extradural group and 26.7 (1.8) b.p.m in the morphine group. Median oxygen

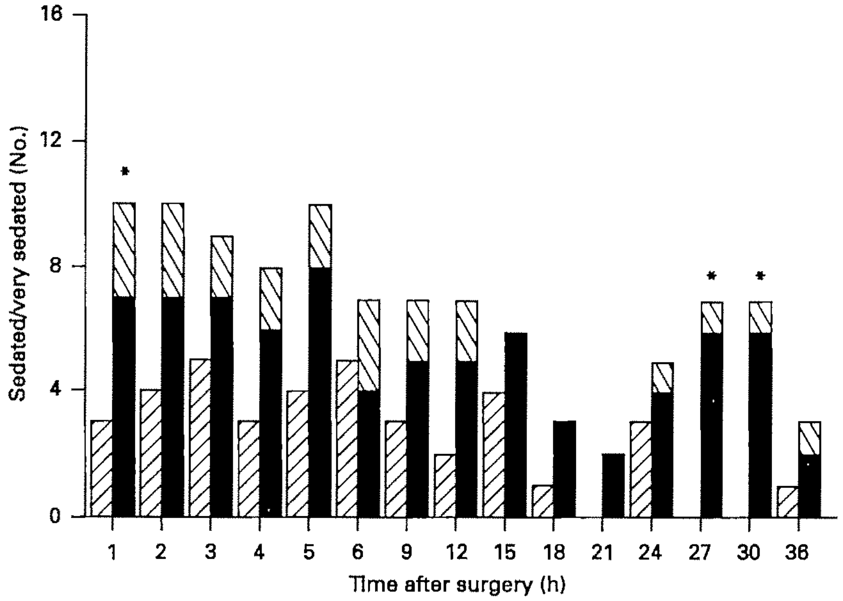


FIG. 3. Comparison of the numbers of patients in the extradural and morphine groups observed as sedated (sedation score 2) or very sedated (sedation score 3) over the first 36 h after operation. ▨ = Bupivacaine group with sedation score 2; ■ = morphine group with sedation score 2; ▧ = morphine group with sedation score 3. $^{*}P < 0.05$.

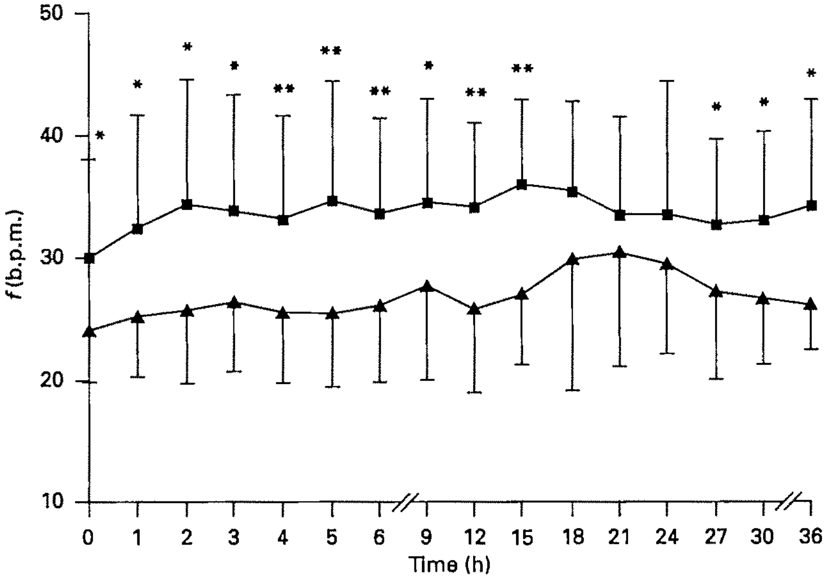


FIG. 4. Ventilatory frequencies (*f*) for patients receiving extradural bupivacaine (■) or morphine (▲) analgesia (mean, SD). $^{*}P < 0.05$; $^{**}P < 0.01$.

saturations and quartiles were 96 (95.2–97) % in the bupivacaine group and 94 (94–94.7) % in the morphine group.

The decreased ventilatory frequencies and oxygenation did not appear to have any clinical consequences in this study and, although the oxygen saturation monitor alarmed occasionally because of disconnection, there were no episodes of major ventilatory depression or apnoea causing desaturation to less than 85 %.

One patient in the extradural group had a dural tap at the time of insertion of the Tuohy needle. After removing the needle, the procedure was repeated without a problem and the caudal catheter inserted. CSF could not be aspirated through the threaded catheter and the patient remained in the study without further complication. The averaged systolic arterial pressure for each patient was significantly less ($P < 0.01$) in the bupivacaine group (97.4 (SD 2.7) mm Hg) than in the morphine group (101.1 (3.6) mm Hg) during surgery, but this difference did not continue in the postoperative period. Mean systolic arterial pressures during the postoperative period were 109.3 (3.7) mm Hg for the extradural group and 110.3 (5.3) mm Hg for the morphine group, and there were no individual problems with hypotension. None of the patients in either group had distressing or persistent vomiting. There was wide variability in the time to first bowel action after surgery, but no difference between treatment groups could be detected: 62.9 (44.8) h for the extradural group and 65.6 (36.3) h in the morphine group. No other major complications or side effects were noted by the nursing staff, except for the comments on

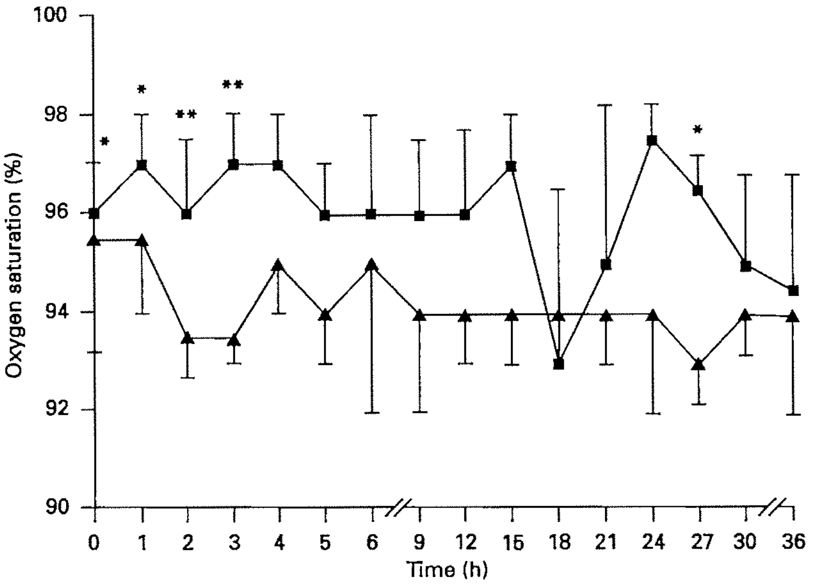


FIG. 5. Oxygen saturation for patients receiving extradural bupivacaine (■) or morphine (▲) analgesia (median, quartiles). $*P < 0.05$; $**P < 0.01$.

restlessness discussed above. The incidence of urinary retention could not be evaluated because 30 of the patients had indwelling urinary catheters.

DISCUSSION

Postoperative analgesia with nurse-administered i.m. opioids still remains the most common method of pain relief after surgery [13], despite the availability of more effective techniques. I.v. morphine infusions have been used in children for some years [8, 14] and are feasible even in infants younger than 6 months [15]. However, the technique is not used commonly outside an intensive care unit in younger age groups because of the risks of ventilatory depression and the requirements for close monitoring. Infusions of extradural bupivacaine [2, 5] can also provide postoperative analgesia in children, but have never been compared with morphine.

A prospective double-blind study comparing extradural bupivacaine with i.v. morphine would not be possible in adults because of the obvious changes in sensation from the local anaesthesia. However, it was achieved in a younger age group because of their limited verbal communication, the lack of motor block from a 0.25 % bupivacaine infusion [2], and by elaborately disguising the technique. In this study, most patients had good analgesia, irrespective of the method used. The distributions of pain scores with time (fig. 1) or by patient (fig. 2) were similar. While the null hypothesis cannot be proven from this study of 32 patients, the results show no major clinical difference in analgesia between the two techniques. It could be argued that the pain scoring system was not sensitive enough to discern differences between the two groups. However, significant differences in pain scores have been recorded in previous studies on the same ward using identical methods [16, 17]. There was no correlation between levels of sedation and pain scores in this study, which was surprising. The unsedated patient can become agitated and rate high pain scores without being in pain. Analgesic techniques, such as i.v. morphine, that produce sedation in addition to pain relief may appear more effective than a non-sedating technique such as extradural bupivacaine because of the reduction in conscious level.

The difference in sedation scores between the two groups was marked. Infants in the extradural group were active much of the time and this was beneficial from the aspect of nursing supervision for ventilatory depression. However, while the lack of sedation made little difference in the infants younger than 6 months, it was more noticeable and occasionally troublesome in the older children (three patients). Overactivity and restlessness have not been reported previously as side effects of extradural analgesia, although they should be expected, particularly in the older and more mobile infants who have little or no pain. This can become a problem for the nursing staff in a busy ward if a child needs supervision to stop it investigating newly placed dressings and drains. Sedation with morphine or diazepam may occasionally be required, to supplement an extradural technique.

The reduced ventilatory frequency and oxygen saturation in those patients receiving morphine were not clinically obvious or important in this study, but may be relevant in the choice of postoperative analgesia for infants with immature ventilatory drive or pre-existing lung disease. Local techniques can eliminate the need for centrally acting drugs that depress ventilation and, used in place of general anaesthesia, may reduce postoperative apnoea in the "at risk" patient [18, 19]. Resting ventilation is reduced after extradural analgesia, but the ventilatory response to carbon dioxide is enhanced [20] and this may be protective, particularly in the early postoperative period. Extradural bupivacaine may, therefore, be a desirable alternative to opioid analgesia in the infant with ventilatory impairment.

The dose of morphine required to achieve analgesia in this study varied from 5 to 40 $\mu g\ kg^{-1}\ h^{-1}$ and was similar to established treatment regimens for this age group [14]. The initial infusion rate of 5–10 $\mu g\ kg^{-1}\ h^{-1}$ was adequate in the early postoperative period, but required adjustment as the effects of general anaesthesia and the initial loading dose of morphine decreased. Greater initial rates of infusion of i.v. morphine might have improved analgesia after 12 h, but would have increased sedation and ventilatory depression in the early postoperative period. In both groups, alteration of the infusion rates achieved pain control, but there was an inevitable lag between increasing the infusion rates and reduction in pain scores. Single additional doses of i.v. morphine or extradural morphine would have produced more immediate analgesia, but were not possible within the blinded study design.

Desparmet and colleagues [5] have used infusions of 0.25% bupivacaine via a lumbar extradural catheter in children undergoing urogenital or lower limb surgery and reported adequate analgesia with an infusion rate of 0.08 $ml\ kg^{-1}\ h^{-1}$. In our study, an initial infusion rate of bupivacaine 0.1 $ml\ kg^{-1}\ h^{-1}$ had to be increased in all but three patients to maintain adequate analgesia; a starting infusion rate of 0.15 $ml\ kg^{-1}\ h^{-1}$ might have been more appropriate. The differences in our results may reflect that our patients were younger, that they underwent abdominal surgery and that a different technique was used for catheter insertion. Unlike local anaesthetic extradural infusions in adults [21], bupivacaine infusions in infants produce stable levels of analgesia [5] and can produce an ascending block [9]. Periodic pinch tests should be undertaken to ensure that the block is not extending to too high a level. Infusions of extradural bupivacaine also have the potential to cause toxicity from systemic accumulation, but the risk appears to be low when appropriate infusion schemes are used [5].

Cannulation of the extradural space by the caudal route is technically less difficult than the lumbar route in small infants, but the risk of contamination and potential for infection may be greater because of close proximity to the perineum. A lumbar approach is generally preferable, but the choice of route depends on the size of the infant and expertise of the anaesthetist. In this study, all catheters were taped away from the perineum with waterproof dressings and removed within 3 days of insertion. We are not aware of any reported cases of infection caused by indwelling caudal catheters, but published experience with this technique remains limited. Long-term use of caudal catheters would be contraindicated unless they were tunnelled s.c.

Extradural morphine is used for postoperative analgesia in children, but can cause sudden and late onset and sometimes sudden ventilatory depression [22, 23]. Combining opioids and local anaesthetics in an extradural mixture may lessen the risks by reducing individual doses of the drugs and their side effects [16, 17], but younger infants still require intensive monitoring. Extradural infusions of bupivacaine, combined if necessary with small incremental doses of i.v. morphine for additional analgesia and sedation, may be more appropriate in these patients and help avoid the need for a stay in the intensive care unit. Our current clinical practice is to give infants older than 6 months undergoing abdominal surgery an intraoperative dose of i.v. morphine 0.05–0.1 $mg\ kg^{-1}$ or fentanyl 0.5–2 $\mu g\ kg^{-1}$ in addition to extradural analgesia with 0.25% bupivacaine. The analgesia and sedation from the single dose of opioid helps to prevent restlessness in the early postoperative period.

In conclusion, extradural analgesia with bupivacaine given via a caudal catheter provided excellent postoperative analgesia in infants after abdominal surgery. It may be preferable to a morphine infusion in neonates and younger infants who are particularly sensitive to ventilatory depression and in whom sedation is neither necessary or desirable. Older children may require additional sedation or analgesia with this techniques to prevent restlessness in the postoperative period.

REFERENCES

1. Anand KJS, Hickey PR. Pain and its effects on the human neonate and fetus. *New England Journal of Medicine* 1987; **21**: 1321–1329.
2. Murat I, Delleur MM, Esteve C, Egu JF, Raynaud P, Saint-Maurice C. Continuous extradural anaesthesia in children: clinical haemodynamic implications. *British Journal of Anaesthesia* 1987; **69**: 1441–1450.
3. Murat I, Walker J, Esteve C, Nahoul K, Saint-Maurice C. Effect of lumbar epidural anaesthesia on plasma cortisol levels in children. *Canadian Journal of Anaesthesia* 1988; **35**: 20–24.
4. Dupont D, Velin P, Cabour F, Candiot M, Rives E. Effect of caudal anaesthesia on catecholamine secretion in children. *Annales Françaises d'Anesthésie et de Réanimation* 1987; **6**: 1156–1158.
5. Desparmet J, Meistelman C, Barre J, Saint-Maurice C. Continuous epidural infusion of bupivacaine for postoperative pain relief in children. *Anesthesiology* 1987; **67**: 108–110.
6. Bosenberg AT, Bland BAR, Schulte-Steinberg O, Downing JW. Thoracic epidural anesthesia via caudal route in infants. *Anesthesiology* 1988; **69**: 265–269.
7. Rasch DK, Webster DE, Pollard TG, Gurkowski MA. Lumbar and thoracic analgesia via the caudal approach for postoperative pain relief in infants and children. *Canadian Journal of Anaesthesia* 1990; **37**: 359–362.
8. Dilworth NM, MacKellar A. Pain relief for the pediatric surgical patient. *Journal of Pediatric Surgery* 1987; **22**: 264–266.
9. Wolf AR, Walker SM. Development of a high block in an infant during an epidural bupivacaine infusion. *Anaesthesia and Intensive Care* 1991; **19**: 583–585.
10. Tucker GT, Cooper S, Littlewood D, Buckley FP, Covino GB, Scott DB. Observed and predicted accumulation of local anaesthetic agents during continuous extradural analgesia. *British Journal of Anaesthesia* 1977; **49**: 237–241.
11. Takasaki M, Dohi S, Kawabata Y, Takahashi T. Dosage of lidocaine for caudal anesthesia in infants and children. *Anesthesiology* 1977; **47**: 527–529.
12. Hanallah RS, Broadman LM, Belman AB, Abromowitz MD, Epstein BS. Comparison of caudal and ilioinguinal/iliohypogastric nerve blocks for the control of post-orchidopexy pain in pediatric ambulatory surgery. *Anesthesiology* 1987; **66**: 832–834.
13. Semple P, Jackson IJB. Postoperative pain control: a survey of current practice. *Anaesthesia* 1991; **46**: 1074–1076.
14. Lloyd-Thomas AR. Pain management in paediatric patients. *British Journal of Anaesthesia* 1990; **64**: 85–104.
15. Jones SEF, Stokes MA. Papaveretum infusions in infants under 6 months of age. *Anaesthesia* 1991; **46**: 688–690.
16. Wolf AR, Hughes D, Wade A, Mather SJ, Prys-Roberts C. Postoperative analgesia after paediatric orchidopexy: evaluation of a bupivacaine–morphine mixture. *British Journal of Anaesthesia* 1990; **64**: 430–435.

17. Wolf AR, Hughes D, Hobbs AJ, Prys-Roberts C. Combined morphine–bupivacaine caudals for reconstructive penile surgery in children: systemic absorption of morphine and postoperative analgesia. *Anaesthesia and Intensive Care* 1991; **19**: 17–21.
18. Meignier M, Souron R, LeNeel JC. Postoperative dorsal epidural analgesia in the child with respiratory disabilities. *Anesthesiology* 1983; **59**: 473–475.
19. Welborne LG, Rice JR, Hannallah RS, Broadman LM, Ruttiman UE, Fink R. Postoperative apnea in former preterm infants: prospective comparison of spinal and general anesthesia. *Anesthesiology* 1990; **72**: 838–842.
20. Takasaki M. Ventilation and ventilatory response to carbon dioxide during caudal anaesthesia with lidocaine or bupivacaine in sedated children. *Acta Anaesthesiologica Scandinavica* 1988; **32**: 218–221.
21. Hjortso NC, Lund C, Mogensen T, Bigler D, Kehlet H. Epidural morphine improves pain relief and maintains sensory analgesia during continuous epidural bupivacaine after abdominal surgery. *Anesthesia and Analgesia* 1986; **65**: 1033–1036.
22. Krane EJ, Tyler DC, Jacobson LE. The dose response of caudal morphine in children. *Anesthesiology* 1989; **71**: 48–52.
23. Valley RD, Bailey AG. Caudal morphine for postoperative analgesia in infants and children: a report of 138 cases. *Anesthesia and Analgesia* 1991; **72**: 120–124.

British Journal of Anaesthesia 1993; **70**: 17–21

EXTRA INSPIRATORY WORK OF BREATHING IMPOSED BY CRICOTHYROTOMY DEVICES†

R. OOI, W. J. FAWCETT, N. SONI AND B. RILEY

SUMMARY

Using a lung model for spontaneous ventilation, we have assessed the additional work of inspiration imposed by a variety of cannulae ranging from the 12- and 14-gauge intravascular cannulae to the 8.0-mm i.d. adult tracheostomy tube. Work (W) ranged between 9 and 2262 mJ litre^{-1} and power ($\dot{W}$) between 0.2 and 37.7 mW litre^{-1} min; the smallest values were obtained with the 8.0-mm i.d. adult tracheostomy tube and the 12- and 14-gauge intravascular cannulae gave the largest values. With any given cannula, W and $\dot{W}$ were influenced by ventilation (tidal volume and frequency) and ventilatory wave pattern of the analogue lung. The results obtained from the 12- and 14-gauge cannulae represent what is probably an excessive inspiratory workload, whereas the other four devices (Portex MiniTrach, 4.0, 6.0 and 8.0 tracheostomy tubes) may be suitable in the short term for relieving airway obstruction and compatible with spontaneous ventilation. (Br. J. Anaesth. 1993; **70**: 17–21)

KEY WORDS

Equipment: tracheostomy tubes. Ventilation: inspiratory work.

Percutaneous cricothyrotomy is an important technique in the emergency management of upper airway obstruction. A wide range of cannulae have been considered as suitable for this procedure under emergency conditions. Generally, oxygen at positive pressure is administered either by intermittent positive insufflation or by jet ventilation. It is conceivable that, under some circumstances, the facilities to provide this type of positive pressure support may be unavailable and spontaneous ventilation has been advocated. If this is to be successful, the standard resuscitation manuals advocate the insertion of a large-bore cannula of at least 5.0 or 6.0-mm i.d. in adults [1, 2], but this demands more technical expertise.

The aim of the present study was to assess a variety of cannulae that may be available for percutaneous cricothyrotomy. Previous studies of the impact of external resistance on breathing have used continuous gas flows and calculated resistance by measuring driving pressures across the airway [3–5]. However, the results of resistance are difficult to relate to the clinical situation. This study avoided such criticisms by following Mecklenburgh and colleagues [6] and measuring the additional work of inspiration required if spontaneous ventilation is attempted through any of the cannulae.

MATERIALS AND METHODS

The cannulae under study were as follows: 12-gauge Medicut and 14-gauge Abbocath intravascular catheters attached by 3.5-mm tracheal tube connectors, the 4.0-mm i.d. minitracheotomy tube (Portex, MiniTrach) and the 4.0-, 6.0- and 8.0-mm i.d. Portex tracheostomy tubes. Duplicate samples of each device were tested.

Spontaneous ventilation was simulated using a lung model [7]. This was connected to each test cannula in turn. In the first part of the study, a modified Cape–Waine ventilator was used to drive the lung model, simulating a sine-wave respiratory flow pattern, with tidal volume settings of 350 and 500 ml, and with a ventilatory frequency (f) of 10, 16 and 20 "breaths" per minute (b.p.m.). The experimental model is shown in figure 1.

In the second part of the study, a "waveform generator", comprising an interlinked pair of bellows (fig. 2) connected to a Nuffield Oxford ventilator, was used to drive the lung model. The inspiration time, as a fraction of the ventilation period (T_I/T_T) was varied between 0.24 and 0.48 while the tidal volume setting of the ventilator was kept at 350 ml and the frequency setting at 16 b.p.m. The apparatus was used to assess the inspiratory workload of the Portex MiniTrach, 4.0-, 6.0- and 8.0-mm i.d. tracheostomy tubes.

The measurements taken in this study were airway

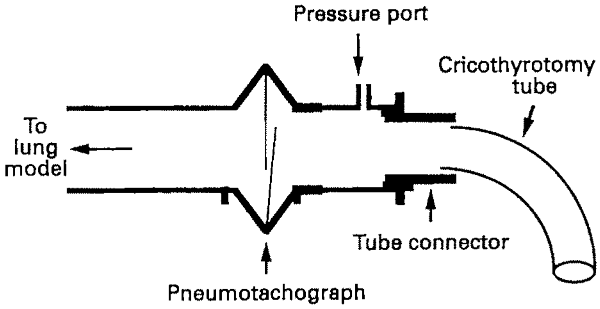


FIG. 1. Schematic diagram of the measurement equipment.

R. OOI, F.R.C.ANAES.; W. J. FAWCETT, F.R.C.ANAES.; N. SONI, F.F.A.R.A.C.S.; B. RILEY, M.B.E., F.R.C.ANAES.; Magill Department of Anaesthesia, Westminster Hospital, London SW1P 2AP.
Accepted for Publication: August 5, 1992.
† With an Appendix by W. W. Mapleson.

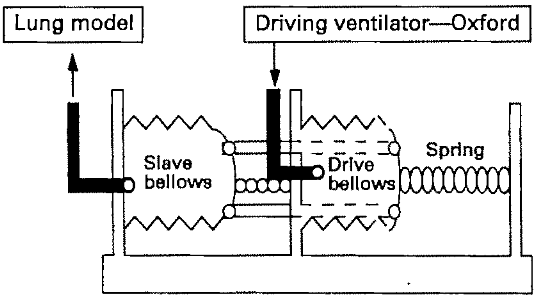


FIG. 2. Waveform generator to inter-link lung model and driving ventilator. Inflation of drive bellows results in negative pressure exerted in the coupled slave bellows, resulting in inspiration.

pressure (P) and ventilatory flow ($\dot{v}$). P was measured immediately proximal to the cannula using a pressure transducer (Scientific Electro Systems, 170 PC) and $\dot{v}$ was measured using a variable orifice pneumotachograph (Accutach, McGaw Respiratory Therapy) attached to a differential pressure transducer (Scientific Electro Systems, 170 PC). The airway pressure transducer was calibrated using a water manometer and the pneumotachograph was calibrated in air using rotating bobbin flowmeters (Gap-meter, A_6 and A_{10}). The pressure and flow signals were digitized at 200 Hz onto a computer chart recorder program.

It is common to speak of the "work of breathing". However, breathing is a continuous process over time. Therefore, strictly, it is appropriate to refer only to the work of one breath or to the power (rate of working) of breathing. The mathematical equation described by Engstrom and Norlander [8] was used to calculate the additional work of one breath:

$$\int_{t_1}^{t_2} P.\dot{v}dt$$

that is, the integral of $P.\dot{v}$ during the inspiratory phase from t_1 to t_2, where P is the instantaneous pressure change across the cannula and $\dot{v}$ the instantaneous flow through it. This additional inspiratory work (W) was expressed in mJ/litre tidal volume. The additional inspiratory power of breathing (J s^{-1} or Watts ($\dot{W}$)) is the inspiratory work of one breath divided by the respiratory period. It is expressed in Watts per litre min^{-1} of total ventilation. These values of work and power were averaged over six successive breaths.

RESULTS

In the first part of the study, when the sine-wave ventilatory pattern was used (tables I, II), W ranged from 9 to 2262 mJ litre^{-1} and $\dot{W}$ from 0.2 to 37.7 mW litre^{-1} min. Peak pressure ($\hat{P}$), W and $\dot{W}$ increased progressively as successively narrower tubes were used, even though tidal volume decreased in the process. $\hat{P}$, W and $\dot{W}$ also increased with frequency and tidal volume.

In the second part of the study, the waveform generator produced a ramp waveform (fig. 3). Again, $\hat{P}$, W and $\dot{W}$ increased as progressively narrower tubes were used (table III), but they decreased as the fraction of the ventilatory cycle assigned to inspiration was increased from 0.24 to 0.48.

In both parts of the study, the results were consistent when the measurements were repeated with the second set of transtracheal devices; the maximum discrepancy was less than 2%.

DISCUSSION

The normal power of breathing has been quoted as 70 mW [9]. For a total ventilation of 5–8 litre min^{-1}, this is 9–14 mW litre^{-1} min. It has also been reported

TABLE I. *Work* (W) *and power* ($\dot{W}$) *expenditure on different tubes during simulated ventilation* (*sine wave respiratory flow from Cape–Waine ventilator set at a tidal volume of 500 ml*) *at various ventilatory frequencies* (f) *and measured tidal* (V$_T$) *and minute volumes* ($\dot{V}$). *T8 = adult 8.0-mm i.d. tracheostomy tube; T6 and T4 = paediatric 6.0- and 4.0-mm i.d. tracheostomy tubes; MT = Portex MiniTrach (4.0 mm i.d.), 12G and 14G = 12- and 14-gauge intravascular cannulae.* $\hat{P}$ = *Peak pressure* (*negative direction*) *during inspiration*

Tube	f (b.p.m.)	V_T (ml)	$\dot{V}$ (litre min^{-1})	$\hat{P}$ (Pa)	W (mJ litre^{-1})	$\frac{W}{\hat{P}}$	$\dot{W}$ (mW litre^{-1} min)
T8	10	571	9.71	−30	18	0.6	0.3
T6	10	564	5.64	−100	62	0.62	1.0
T4	10	559	5.59	−420	293	0.70	4.9
MT	10	556	5.56	−590	406	0.69	6.8
12G	10	378	3.78	−2170	1640	0.76	27.3
14G	10	229	2.29	−2740	2153	0.79	35.9
T8	16	523	8.37	−50	34	0.68	0.6
T6	16	522	8.35	−200	125	0.62	2.1
T4	16	503	8.05	−770	523	0.68	8.4
MT	16	501	8.02	−1020	709	0.70	11.8
12G	16	263	4.21	−2450	1837	0.75	30.6
14G	16	153	2.45	−2880	2255	0.78	37.6
T8	20	509	10.18	−70	49	0.7	0.8
T6	20	506	10.12	−270	174	0.64	2.9
T4	20	487	9.24	−970	680	0.70	11.3
MT	20	472	9.44	−1270	898	0.71	16.7
12G	20	222	4.44	−2550	1937	0.76	37.0
14G	20	126	2.52	−2880	2262	0.79	37.7

TABLE II. *Work and power expenditure (as in table I except for a set tidal volume of 350 ml)*

Tube	f (b.p.m.)	V_T (ml)	$\dot{V}$ (litre min^{-1})	$\hat{P}$ (Pa)	$\bar{W}$ (mJ litre^{-1})	$\frac{\bar{W}}{\hat{P}}$	$\dot{\bar{W}}$ (mW litre^{-1} min)
T8	10	427	4.27	−20	9	0.45	0.2
T6	10	426	4.26	−50	35	0.70	0.6
T4	10	424	4.24	−260	180	0.69	3.0
MT	10	420	4.20	−369	257	0.71	4.3
12G	10	304	3.04	−1570	1188	0.76	23.7
14G	10	183	1.83	−2090	1634	0.78	32.7
T8	16	392	3.92	−30	20	0.67	0.3
T6	16	390	3.90	−110	69	0.63	1.2
T4	16	383	3.83	−460	316	0.69	5.3
MT	16	380	3.80	−630	437	0.69	7.3
12G	16	218	2.18	−1780	1349	0.76	22.5
14G	16	120	1.20	−2110	1658	0.79	27.6
T8	20	380	3.80	−50	29	0.58	0.5
T6	20	378	3.78	−170	108	0.64	1.8
T4	20	366	3.66	−650	445	0.68	7.4
MT	20	357	3.57	−860	602	0.70	10.0
12G	20	177	1.77	−1890	1441	0.76	24.0
14G	20	94	0.94	−2150	1702	0.79	28.4

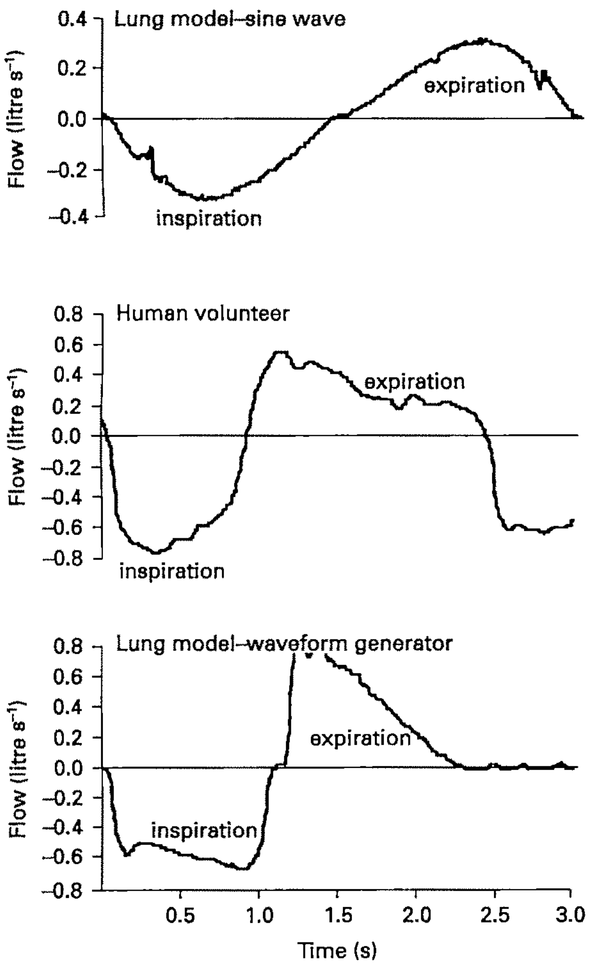


FIG. 3. Ventilatory flow recordings taken from a human subject (breathing through a Mapleson A–Magill system at 6 litre min^{-1}) and from a lung model (using the Cape–Waine and waveform generator attachment).

that few patients can sustain spontaneous ventilation when $\dot{\bar{W}}$ is 300–400% of normal [10]—that is, additional power of 18–42 mW litre^{-1} min. As the 12- and 14-gauge cannulae required an additional 30–40 mW litre^{-1} min, even at a ventilation of only 2.5 litre min^{-1}, they are clearly unsatisfactory for sustained use, although there has been a report of satisfactory use of two 12-gauge cannulae together [11]. In contrast, the wider tubes impose much lighter loads on breathing. The MiniTrach required 3.4–16.7 mW litre^{-1} min (30–190% of normal), for up to 9.4 litre min^{-1} ventilation. This suggests that, although designed primarily for tracheobronchial toilet, this device may provide a satisfactory temporary airway before provision of a definitive airway. For the 4.0- and 6.0-mm i.d. paediatric tracheostomy tubes, the loads range between 20–130% and 3–33% of normal, respectively. For comparison, the adult 8.0-mm i.d. tracheostomy tube imposed 1–10% of normal.

With the sine-wave flow from the Cape–Waine ventilator, the tidal volume decreased as progressively larger loads were applied (tables I, II). Fortuitously, this may reflect how a patient would respond when expected to breathe through these cannulae. This would lead to carbon dioxide retention and hypoxaemia.

As the resistance of the cannulae, and the flows through them, increase, it is to be expected that $\hat{P}$, $\bar{W}$ and $\dot{\bar{W}}$ increase. Tables I–III show that there is a limited range of the ratio $\bar{W}:\hat{P}$. This can be explained theoretically. Thus, if inspiratory flows were constant throughout inspiration, and laminar, and if tidal volume was doubled, the flow and the pressure difference ($\hat{P}$) would also increase by a factor of 2. Work, the integral of flow times pressure, would increase by a factor of 4. Therefore $\bar{W}$ (work per litre of tidal volume) would increase by a factor of 2, and $\bar{W}:\hat{P}$ by a factor of 1: the ratio would be unaltered. If the flows were constant but turbulent, doubling the tidal volume would increase $\hat{P}$ by a factor of 4, and work by a factor of 8. Therefore $\bar{W}$ would increase by a factor of 4; but $\bar{W}:\hat{P}$ would again be unaltered. A similar argument shows that $\bar{W}:\hat{P}$ is

TABLE III. *Effect of altering inspiratory time (T_I/T_T) with the waveform generator (figs 2 and 3) on the inspiratory work (W) and power ($\dot{W}$). Tidal volume was set at 350 ml and ventilatory frequency was 16 b.p.m. T8 = 8.0-mm i.d. adult tracheostomy tube; T6 and T4 = paediatric 6.0-mm and 4.0-mm i.d. tracheostomy tubes; MT = Portex MiniTrach*

Tube	T_I/T_T	V_T (ml)	$\dot{V}$ (litre min^{-1})	$\hat{P}$ (Pa)	W (mJ litre^{-1})	$\dot{W}$ (mW litre^{-1} min)	$\frac{W}{\hat{P}}$
T8	0.24	331	5.30	−50	30	0.5	0.60
T6	0.24	342	5.45	−150	94	1.6	0.63
T4	0.24	337	5.39	−510	335	5.6	0.66
MT	0.24	335	5.36	−700	457	7.6	0.65
T8	0.29	333	5.33	−40	22	0.4	0.55
T6	0.29	350	5.60	−120	67	1.1	0.56
T4	0.29	336	5.38	−420	277	4.6	0.66
MT	0.29	353	5.65	−570	368	6.1	0.65
T8	0.37	336	5.38	−30	16	0.3	0.53
T6	0.37	340	5.44	−80	45	0.8	0.55
T4	0.37	366	5.86	−300	203	3.4	0.68
MT	0.37	297	4.75	−200	270	4.5	0.67
T8	0.48	336	5.38	−20	10	0.2	0.50
T6	0.48	350	5.60	−50	31	0.5	0.62
T4	0.48	364	5.82	−200	137	2.3	0.69
MT	0.48	360	5.76	−300	200	3.4	0.67

also independent of frequency. In the present experiments, $W:\hat{P}$ was consistently less than 1, but flow was not constant. However, it can be shown (see Appendix) that, for sine-wave flow, with a 1:1 I:E ratio (as for tables I and II), $W:\hat{P}$ should be $\pi/4$ (0.78) for laminar flow and 2/3 (0.67) for fully turbulent flow, irrespective of tidal volume and frequency. If allowance is made for the inaccuracies in $W:\hat{P}$ that arise when $\hat{P}$ is small, this suggests that flow was laminar through the 12- and 14-gauge cannulae, but turbulent through the wider tubes.

With the waveform generator, driven by the Nuffield Oxford ventilator, the tidal volume was nearly constant for the range of tubes studied (table III). Here, the reduction in W and $\dot{W}$ as T_I/T_T was increased (at constant frequency) can be attributed to the reduction in peak flow and, hence, in $\hat{P}$.

In conclusion, the 12- and 14-gauge cannulae represent what is probably an excessive inspiratory workload, whereas the other four devices may be suitable in the short-term for relieving airway obstruction. Given the familiarity of anaesthetists in intensive care in inserting the MiniTrach, these findings suggest that this device may have a role in the management of airway obstruction. The 6.0-mm i.d. paediatric tracheostomy tube would provide the least additional work of breathing for a cannula compatible with easy insertion by cricothyrotomy.

APPENDIX

THEORETICAL VALUE FOR $W:\hat{P}$ WITH SINE-WAVE FLOW

For laminar flow through a resistance, $p = k.\dot{v}$ (1)
where p = instantaneous pressure difference across the resistance; $\dot{v}$ = instantaneous flow through it; k = a constant.

Instantaneous power (rate of doing work on the resistance) is given by:

$$\dot{w} = p\dot{v}$$

therefore,

$$\dot{w} = k\dot{v}^2 \tag{2}$$

For sine-wave flow, with an I:E ratio of 1:1,

$$\dot{v} = \hat{\dot{v}}\sin(2\pi ft) \tag{3}$$

where $\hat{\dot{v}}$ = peak flow, f = frequency of the sine-wave (ventilatory frequency), and t = time from start of the inspiratory sine wave.

The work done during inspiration is given by:

$$W_I = \int_0^{1/2f} \dot{w}\,dt \tag{4}$$

Substituting (2) and (3) in (4) gives:

$$W_I = k\hat{\dot{v}}^2 \int_0^{1/2f} \sin^2(2\pi ft)\,dt \tag{5}$$

Expressing the progress of a sine-wave in terms of angle, θ, instead of time t (from the start of the sine-wave) gives:

$$\theta = 2\pi ft \tag{6}$$

whence

$$dt = 2\pi ft\,d\theta/2\pi f \tag{7}$$

also, when $t = 1/2f, \theta = \pi$. (8)

Using (6), (7) and (8) in (5) gives:

$$W_I = (k\hat{\dot{v}}/2\pi f)\int_0^{\pi} \sin^2\theta\,d\theta$$

Using integral 296 from Weast [12], and equation (1), this integrates to:

$$W_I = \hat{P}\hat{\dot{v}}/4f$$

where $\hat{P}$ is the peak pressure difference across the resistance.

However, for a 1:1 sine wave, it can be shown that

$$\hat{\dot{v}} = \pi V_T f,$$

where V_T is the tidal volume. Therefore,

$$W_I = \hat{P}\pi V_T/4,$$

but the work per litre $W = W_I/V_T$. Therefore

$$\frac{W}{\hat{P}} = \frac{\pi}{4} = 0.78$$

For fully turbulent flow through the resistance,

$$p = k\dot{v}^2$$

A parallel analysis, using integral 297 from Weast [12], leads to

$$\frac{W}{\hat{P}} = \frac{2}{3} = 0.67$$

W. W. Mapleson

ACKNOWLEDGEMENT

This work was carried out while R. O. was a Smiths Industries Medical Systems Research Fellow.

REFERENCES

1. Safar P (ed.). *Airway Control*, 3rd Edn. London: W. B. Saunders, 1988; 59–60.
2. Baskett PJF. *Resuscitation Handbook.* London: Gower, 1989; 27–29.
3. Fisher J. A "Last Ditch" Airway. *Canadian Anaesthetists Society Journal* 1979; **26**: 225–230.
4. Attia RR, Battit GE, Murphy JD. Transtracheal ventilation. *Journal of the American Medical Association* 1975; **234**: 1152–1153.
5. Bougas TP, Cook CD. Pressure–flow characteristics of needles suggested for transtracheal resuscitation. *New England Journal of Medicine* 1960; **262**: 511–513.
6. Mecklenburgh JP, Latto IP, Al-Obaidi TAA, Swai EA, Mapleson WW. Excessive work of breathing during intermittent mandatory ventilation. *British Journal of Anaesthesia* 1986; **58**: 1048–1054.
7. Chan ASH, Bruce WE, Soni NC. A comparison of anaesthetic breathing systems during spontaneous ventilation. *Anaesthesia* 1989; **44**: 194–199.
8. Engstrom CG, Norlander OP. A new method for analysis of respiratory work by measurements of the actual power as a function of gas flow, pressure and time. *Acta Anaesthesiologica Scandinavica* 1962; **6**: 49–55.
9. Proctor HJ, Woolson R. Prediction of respiratory muscle fatigue by measurements of the work of breathing. *Surgery, Gynecology and Obstetrics* 1973; **136**: 367–370.
10. Fiastro JF, Habib NP, Quan SF. Comparison of standard weaning parameters and the mechanical work of breathing in mechanically ventilated patients. *Chest* 1988; **94**: 232–238.
11. Dallen LT, Wine R, Benumof JL. Spontaneous ventilation via transtracheal large bore intravenous catheters is possible. *Anesthesiology* 1991; **75**: 531–533.
12. Weast RC (ed.). *CRC Handbook of Chemistry and Physics*, 67th Edn. Boca Raton, Florida: CRC Press, 1986; A-38.

British Journal of Anaesthesia 1993; 70: 22–24

EVIDENCE FOR DYNAMIC PHENOMENA IN RESIDUAL TRACHEAL TUBE BIOFILM

T. J. J. INGLIS

SUMMARY

It has been proposed recently that a dynamic physical process occurring in the tracheal tube might account for the dissemination of bacteria and biofilm fragments into the lungs during mechanical ventilation, and the subsequent development of ventilator-associated pneumonia. In this study of tracheal tubes from consecutive adult intensive care patients, biofilms were detected radiographically in 45 of 50 tubes, and were found at the lower end of the tube more often than at the upper end ($P < 0.005$). In 37 of 50 tracheal tubes, the maximum biofilm thickness was equal to or greater than the 0.5 mm required for gas–liquid interaction in a tube with an i.d. of 8.5 mm. In 23 of 50 tubes, wave-like patterns were found. Five tubes had no biofilm inside the bevelled tip and another six showed evidence of biofilm loss for a greater distance from the tip. These observations suggest that the distribution of tracheal tube biofilm is caused at least in part by dynamic phenomena in the tracheal tube. (Br. J. Anaesth. 1993; **70**: 22–24)

KEY WORDS

Bacteria: biofilm deposition. Equipment: tracheal tube. Intensive care.

The "biofilm" or fluid layer lining found in tracheal tubes after several hours of use has been implicated as a potential source of bacteria that subsequently colonize the mechanically ventilated lung [1]. Dissemination from the fluid lining layer during ventilator gas flow has been demonstrated *in vitro*, and evidence presented in support of bacterial dissemination from the tracheal tube *in vivo* [2]. More recently, simulation experiments with adult tracheal tubes have led to the proposal that gas–liquid interaction inside the tube might result in dissemination of contaminated fluid particles into the ventilated lung [3].

This phenomenon was explored further by radiographic examination of the distribution of residual luminal biofilm in a series of tracheal tubes.

MATERIALS AND METHODS

Tracheal tubes were collected from consecutive adult patients in a general medical–surgical Intensive Care Unit, and kept in a horizontal position at 4 °C before transit and storage at −20 °C. Refrigeration lasted 1–18 h and transit 5–15 min. The above approach was taken in order to minimize any redistribution of luminal biofilm, and to prevent any deterioration caused by bacterial growth. The outer surface of each tube was cleaned with cotton wool and ethyl alcohol, and each end was sealed with parafilm immediately before storage at −20 °C. After removal from −20 °C storage, each tube was allowed to thaw until the biofilm surface was moist, whereupon approximately 5 g of zinc metal powder (BDH, Poole, Dorset) was tipped into the tube, to excess. The tube was occluded at both ends, upended twice and rotated gently around its longitudinal axis to ensure that the fine powder had covered the entire luminal surface of the tube. Non-adhering powder was removed by gently tapping the lower end of the tube on a flat horizontal surface. Each tube was then wrapped in damp blotting paper and placed in a self-seal polythene bag to prevent further drying.

Tracheal tubes were radiographed immediately in two longitudinal views at 90° to each other, using a decreasing load generator at 50 kV and 2.5 mA (M100, Phillips Medical Systems, Leeds), a Quanta Detail screen set for fine focus (FFD 100, Dupont, Stevenage) and Chronex 7 radiographic film (Dupont).

Radiographs were viewed against a single coldlight viewing box on one occasion, and biofilm thickness measured with micrometer dialgauge callipers (Camlab, Cambridge). Biofilm distribution was measured against a Magill curve template (fig. 1), and recorded when a black negative image was observed between the tracheal tube wall and the luminal zinc coating.

RESULTS

A residual biofilm was present in all but five of the 50 tracheal tubes examined radiographically. Biofilm distribution was complex; nevertheless, some common features were apparent. The proportion of

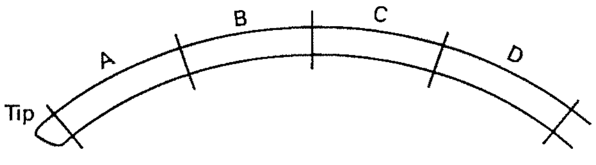


FIG. 1. Magill curve template used to record biofilm distribution.

TIMOTHY J. J. INGLIS, B.M., D.M., M.R.C.PATH, D.T.M.H., Department of Microbiology, University of Leeds, Leeds LS2 9JT. Accepted for Publication: July 17, 1992.

TABLE I. *Distribution of luminal biofilm in tracheal tubes.* $\chi^2 = 56.27$; *d.f.* $= 3$; $P < 0.005$

Tube section	Biofilm absent	Biofilm present
A	5	45
B	13	37
C	22	28
D	46	14

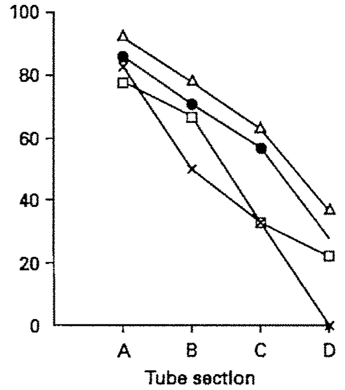


FIG. 2. Distribution of biofilm in tracheal tubes in relation to duration of use (● = < 12 h; △ = 12 h–1 day; □ = 1–5 days; × = > 5 days.

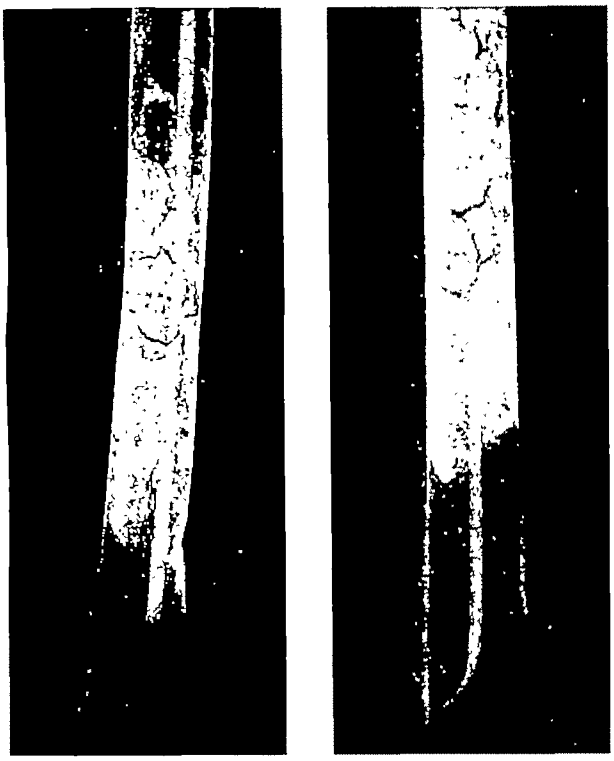


FIG. 3. Radiographic appearance of biofilm-free tracheal tube tip region. Left: Biofilm absent from tip only. Right: Biofilm loss extends further up tube.

TABLE II. *Tracheal tube biofilm crests in relation to duration of use*

Duration of tube use	*n*	Crests	(%)
< 12 h	7	2	28
> 12 h–1 day	27	12	48
> 1–5 days	9	5	56
> 5 days	6	4	67

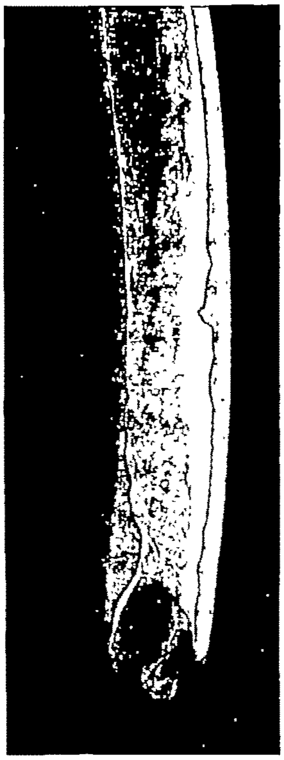


FIG. 4. Wave-like formation in luminal biofilm.

tubes with detectable biofilm decreased progressively from section A near the tip to section D (table I) ($P < 0.005$). In 49 of 50 cases, the duration of tracheal tube was known. The pattern of biofilm distribution was not significantly affected by increased duration of intubation (fig. 2).

Fewer tubes had a biofilm in the region of the bevelled tip than in the adjacent section A. Quantitative analysis of the tip region revealed three different patterns of zinc distribution: present on the inside surface of the bevelled tip (35); absent from only the inside of the bevel (five) (fig. 3A); absent for a greater distance past the bevel (six) (fig. 3B). There was no relationship apparent between these patterns of distribution and duration of intubation.

The maximum thickness of residual biofilm observed was > 0.5 mm in 37 (74%) tracheal tubes. Again, no correlation was found with duration of use.

One or more biofilm crests, similar to waves, were observed in the residual biofilm in 23 (46%) tubes (fig. 4). The proportion of tracheal tubes in which this biofilm formation was observed increased with duration of use, but the relationship was not statistically significant (table II).

DISCUSSION

The tracheal tube has undergone several improvements since it was first introduced, including those designed to reduce tracheal and laryngeal trauma. Less attention has been paid to the design aspects of its principal function as a tubular conduit for inspiratory and expiratory gas flow.

Two decades ago, Clarke and co-workers considered the flow of gas along a narrow bore tube with a viscoelastic fluid lining layer [4]. Their findings indicated that interaction between the gas and liquid phases inside a tube of 8.5 mm i.d. would be expected when the fluid lining layer was 0.5 mm or more. Fragmentation of the luminal surface of the fluid lining layer would be expected to occur at flow rates of 1 litre s^{-1}.

The 0.5-mm minimum thickness required for biofilm surface fragmentation was recorded at some point in the majority of tubes (74 %) examined in the present study. The figure of 74 % may underestimate the probability of biofilm surface fragmentation occurring if the biofilms demonstrated in this study were the residual, or stable remnants, left behind after loss of the more superficial layers.

The *in vitro* experiments referred to above [4] were conducted in a straight tube containing a fluid lining layer of constant viscosity. *In vivo*, the fluid dynamics of the tracheal tube lumen are complicated further by its curvature and by the bevelled end opening into a significantly wider tube. The lower end of the tracheal tube may therefore act as an asymmetrical diffuser [5]. The abrupt inrush of inspiratory phase gas into the proximal tracheal tube, the curvature of the tube and the narrowing of the tube lumen by biofilm may contribute to turbulent flow conditions favourable to biofilm surface fragmentation. It is equally possible that biofilm fragmentation may occur during the expiratory phase of ventilation. The contributions of surface tension effects, biofilm heterogeneity, boundary layers and other fluid phenomena were not examined in this study. Further work on fluid particle dissemination from the tracheal tube should assess the importance of these factors.

This combination of complex dynamic phenomena may explain the efficient scatter of bacteria already demonstrated in simulation experiments [2]. Evidence for dissemination of biofilm fragments during the inspiratory phase of ventilation is more difficult to obtain, but the microscopic particles and viable bacteria described on the patient side of used ventilator filters in the same report [2] are consistent with particle dissemination during expiration.

Although the process of tracheal tube biofilm deposition has yet to be studied in detail, it is presumed to be the result of a progressive accretion of ventilatory secretions. The absence of any clear relationship between maximum thickness and duration of tracheal tube was therefore unexpected. If confirmed in further studies, this suggests that the properties of residual biofilm, the flow conditions prevailing in the tube, or a combination of these factors, conspire to prevent further biofilm deposition.

Flow phenomena sometimes leave behind a permanent record of their occurrence in a more stable or static substratum, such as ripples left in the sand at low tide. The wave-like images seen in views of almost half the tubes examined in this study may represent a similar process. A lesser degree of two-phase flow would induce a slower velocity movement of the more viscous deeper layers of the biofilm. When this occurs near to the bevelled end of the tracheal tube during the inspiratory phase, it would increase the thickness of the fluid lining layer at the point where an asymmetrical diffuser effect may come into play, maximizing the loss of biofilm in this region. The absence of any zinc deposition in this area of maximum expected biofilm deposition, as seen in some tubes, is consistent with extensive biofilm loss.

Fluid dynamics is a largely empirical science, relying on simulation studies and careful observation. The complex dynamic phenomena occurring in the tracheal tubes of patients undergoing mechanical ventilation, reflected in biofilm distribution patterns observed in this study, require further investigation. The results of these investigations should help identify the flow characteristics of the ideal tracheal tube.

ACKNOWLEDGEMENTS

I am grateful to the staff of the Intensive Care Unit, Leeds General Infirmary for their assistance with this study, and to Mrs B. Clough and Dr D. J. Lintott for providing radiographic support.

REFERENCES

1. Sottile FD, Marrie TJ, Prough DS, Hobgood CD, Gower DJ, Webb LX, Costerton JW, Gristina AG. Nosocomial pulmonary infection: possible etiological significance of bacterial adhesion to endotracheal tubes. *Critical Care Medicine* 1986; **14**: 265–270.
2. Inglis TJJ, Millar MR, Jones JG, Robinson DA. Tracheal tube biofilm as a source of bacterial colonization of the lung. *Journal of Clinical Microbiology* 1989; **27**: 2014–2018.
3. Inglis TJJ, Jones JG, Newman SP. Gas–liquid interaction with tracheal tube biofilm as a means of bacterial colonisation of the lung. *British Journal of Hospital Medicine* 1989; **42**: 141–142.
4. Clarke SW, Jones JG, Oliver DR. Resistance to two-phase gas–liquid flow in airways. *Journal of Applied Physiology* 1970; **29**: 464–471.
5. White FM. Experimental duct flows: diffuser performance. In: *Fluid Mechanics*, 2nd Edn. New York: McGraw-Hill, 1987; 345–351.

British Journal of Anaesthesia 1993; 70: 25–29

PRESSURE EXERTED BY THE LARYNGEAL MASK AIRWAY CUFF UPON THE PHARYNGEAL MUCOSA

R. MARJOT

SUMMARY

Ten patients were studied for each of the sizes 2, 3 and 4 laryngeal mask airways (LMA) in order to calculate the pressure exerted by the cuff upon the pharyngeal mucosa. Using a non-invasive method of comparing intracuff pressures recorded both in vitro *and* in vivo, *the transmitted pharyngeal mucosal pressures were calculated over the clinical range of injection volumes. Cuff inflation with the "normal" injection volumes recommended resulted in the residual volumes of the cuffs being exceeded. The intracuff pressures recorded with the mask* in situ *at these normal injection volumes were in the range 103–251 mm Hg. The calculated transmitted mucosal pressures were substantial for all three sizes of cuff and potentially exceeded the capillary perfusion pressure of the adjacent pharyngeal mucosa, despite apparent pharyngeal accommodation to the mask.* (Br. J. Anaesth. 1993; **70**: 25–29)

KEY WORDS

Complications: mucosal pressure. Equipment: laryngeal mask airway.

The laryngeal mask airway (LMA) is an innovative new device for upper airway management. The prototype consisted of an elliptical cuff formed from the black rubber of a Goldman dental mask attached to a tracheal tube [1]. The currently manufactured model is constructed entirely from silicone rubber.

Inflation of the cuff orientates and positions the mask within the pharynx and creates a seal around the laryngeal inlet. This generates a pressure against the adjacent pharyngeal mucosa, sufficient to displace the thyroid and cricoid cartilages anteriorly [2] as the mask is "squeezed out of the triangular shaped base of the hypopharynx" [3].

It has been demonstrated that transmitted lateral wall pressure is the prime determinant of mucosal injury resulting from tracheal tube cuffs [4–6]. There has been one report of phayngeal trauma associated with repeated usage of an LMA within a short period [7]. The manufacturers currently recommend monitoring the LMA intracuff pressures to avoid postoperative throat discomfort [3].

The aim of this study was to determine the pharyngeal mucosal pressures generated by the sizes 2, 3 and 4 LMA with the cuff injection volumes used clinically.

PATIENTS AND METHODS

After Ethics Committee approval, informed written consent was obtained from 30 patients presenting for elective surgery for whom spontaneous ventilation via an LMA was appropriate [3].

The pilot tube of each LMA was attached via a three-way tap to a Spectramed pressure transducer (P10EZ) with a Physio Control VSM 1 recorder, and a Plastipak syringe (fig. 1). A 50-ml and a 10-ml syringe were used for the size 3 or 4 LMA and size 2 LMA, respectively. The same transducer was calibrated against a mercury column and the zero point determined before each study (non-linear error $< 2\%$). Each LMA was suspended in air and the cuff evacuated to a negative pressure of -20 mm Hg. The syringe volumes were adjusted so that they were equal for all the cases in each group of LMA. This was defined as the start point and, when set, this sealed system was not disrupted until the end of each study.

The pilot tube was clamped as it entered the cuff and a pressure–volume curve plotted to enable conversion of injected volume to cuff volume. This was necessary to account for the compression of the air within the inflating syringe, transducer, connecting tubing and pilot tube with pressurization of the system [8] (Appendix). The cuff was then inflated incrementally and the first pressure–volume curve of the cuff recorded (P1). The system was then aspirated back to the start point.

Anaesthesia was induced with propofol 1.5–3 mg kg^{-1} and spontaneous ventilation established with the patient breathing halothane and 67% nitrous oxide in oxygen. The laryngeal mask was inserted according to the manufacturer's instructions [3]. The patient's head and neck were then placed in a neutral position resting upon one pillow. The cuff was inflated incrementally *in situ* to record a second pressure–volume curve (P2).

At the end of surgery, the cuff was deflated *in situ* to record a third pressure–volume curve (P3). The laryngeal mask was removed from the patient and

---

R. MARJOT, M.B., B.S., F.R.C.ANAES., University Department of Anaesthetics, Leicester Royal Infirmary, Leicester LE1 5WW. Present address: Royal United Hospital, Combe Park, Bath BA1 3NG. Accepted for Publication: August 6, 1992.

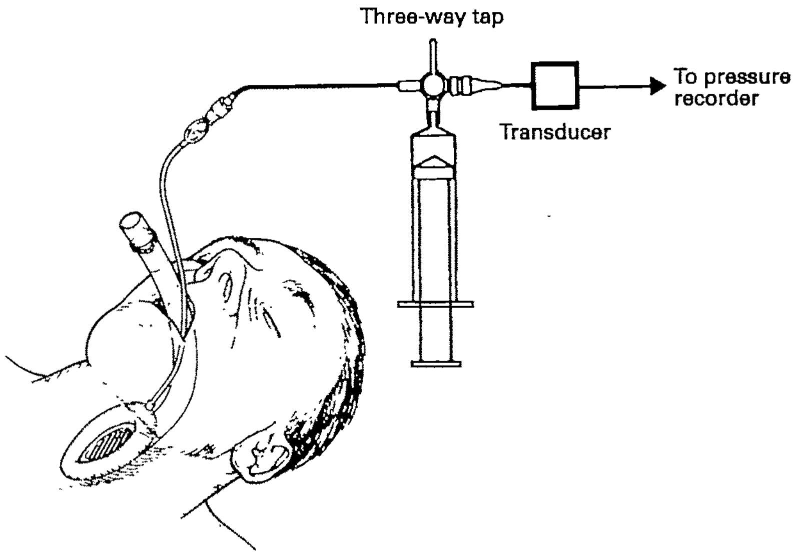


FIG. 1. Diagram of the pressure recording system connected to the laryngeal mask airway *in situ*..

TABLE I. *Patient data (mean (range or* SD*)) and the cuff characteristics for the sizes 2, 3 and 4 laryngeal mask airways*

	Laryngeal mask airways size		
	2	3	4
Age (yr)	3.9 (2–8)	39.1 (10–78)	60.8 (23–84)
Weight (kg)	18.7 (3.9)	57.4 (12)	74.1 (6.9)
Sex (M:F)	7:3	0:10	10:0
Normal injection volume (NIV) (ml)	10	20	30
Cuff volume with NIV (ml)	6.7 (0.2)	14.2 (0.7)	21.8 (1)
Cuff residual volume (ml)	5.5 (0.6)	12.9 (0.9)	17.8 (1.9)
Anaesthetic time (min)	23.2 (10.2)	37 (12.4)	41.5 (16.7)
Cuff volume increase (%)	9 (0.5)	15.4 (7.6)	17.6 (5.2)
Cuff N_2O concn (%)	4.2 (1.3)	10.3 (3.1)	13.1 (4.8)

the cuff immediately reinflated. A fourth pressure–volume curve was recorded with deflation of the cuff whilst it was suspended in air (P4). The cuff was then aspirated back to the start point and the final volume within the syringe recorded.

The pilot tube was again clamped as it entered the cuff and a final pressure–volume curve plotted to enable conversion of injected volume to cuff volume [8] (Appendix). The gas was then aspirated back into the syringe and analysed immediately using a Datex Cardiocap monitor.

Cuff volume was calculated for each injected volume. Each pressure–volume curve (P1–P4) was replotted against cuff volume. Data presented refer to cuff volume.

For each cuff volume, the pharyngeal mucosal pressures for the start ($P\mathrm{pm}_s$) and end ($P\mathrm{pm}_e$) of anaesthesia were calculated. The cuff residual volume is that volume in excess of which the cuff develops sufficient tension itself to generate an intracuff pressure [9]. This intracuff pressure is determined from the pressure–volume curves P1 and P4. In order to obtain the pressure that any given cuff exerts upon the pharyngeal mucosa ($P\mathrm{pm}_s$ and $P\mathrm{pm}_e$), the intracuff pressure resulting from the tension in the cuff itself as its residual volume is exceeded (P1 and P4) is subtracted from the intracuff pressure recorded *in situ* (P2 and P3). Thus:

$$P\mathrm{pm}_s = \mathrm{P2} - \mathrm{P1}$$
$$P\mathrm{pm}_e = \mathrm{P3} - \mathrm{P4}$$

Data were analysed using analysis of variance for repeated measures (MANOVA). Values of $P < 0.05$ were considered significant. Data are presented as mean (SEM).

RESULTS

Observations were recorded for 10 patients using each LMA size (table I). The LMA was inserted successfully at the first attempt in 86% of the cases, and the remainder upon the second attempt. A clinically patent airway was provided in all patients.

Pressure–volume curves

The intracuff pressure increased for all three sizes of LMA with cuff inflation (fig. 2). The pressures recorded were significantly greater with the LMA *in situ* compared with inflation of the cuff whilst it was suspended in air (P2 *vs* P1 and P3 *vs* P4: $P < 0.001$). The cuff itself tended to be more compliant by the end of anaesthesia, but this was not significant (P1 *vs* P4: $P = 0.07$).

The cuff volume resulting from the injection of the manufacturer's "normal" recommended volumes exceeded the cuff residual volume for all three sizes of LMA (table I).

Pharyngeal mucosal pressures

There was an initial increase, followed by a plateau in the calculated transmitted pharyngeal mucosal pressures with increasing cuff volume (fig. 3). The largest calculated mean pharyngeal mucosal pressures were 79.9 (7) mm Hg, 92.3 (6.9) mm Hg and

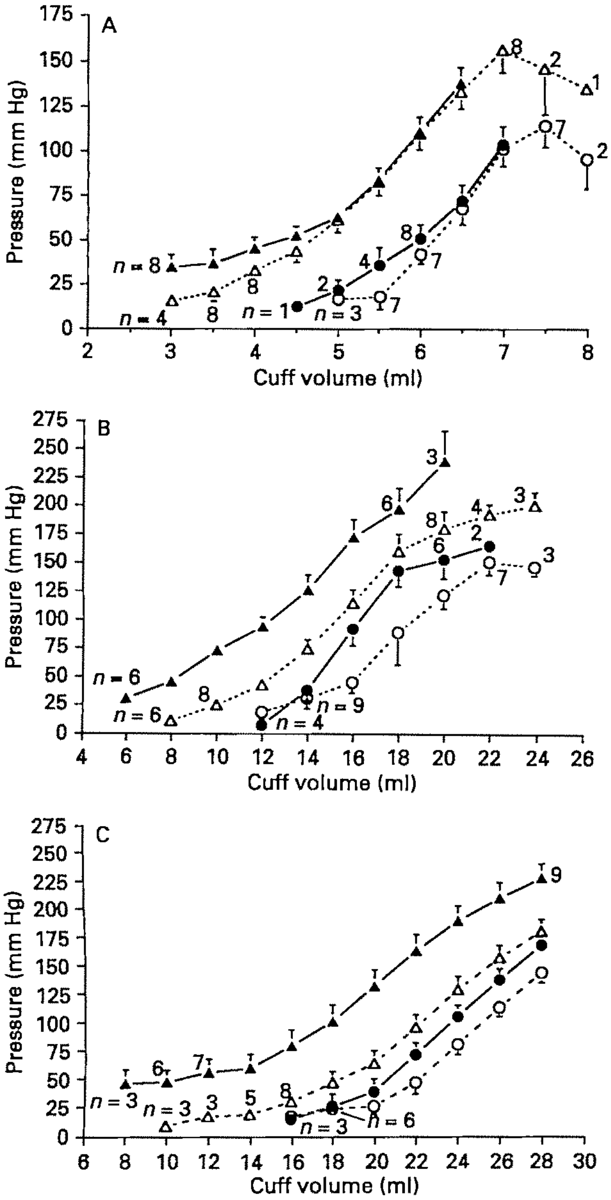


FIG. 2. The pressure–volume curves for P1 (▲), P2 (●), P3 (△) and P4 (○) for (A) size 2, (B) size 3 and (C) size 4 laryngeal mask airways, in 10 patients unless indicated otherwise.

93.1 (9.3) mm Hg for sizes 2, 3 and 4 LMA, respectively.

Using the size 4 LMA, a decrease in transmitted pharyngeal mucosal pressure occurred by the end of anaesthesia (Ppm_e) throughout the range of cuff volumes (fig. 3C). This reduction occurred only at the smaller range of cuff volumes with the sizes 2 and 3 LMA, with no reduction in the largest calculated mean mucosal pressures (fig. 3A, B).

The cuff volume increased in all three LMA groups by the end of anaesthesia. Nitrous oxide was detected in the gas aspirated from the cuffs (table I).

DISCUSSION

Laryngeal mask airway cuff inflation with the normal recommended injection volume [3] results in the residual volume of the cuff being exceeded. At these clinically used injection volumes, the features of a "low residual volume, high pressure cuff" were demonstrated.

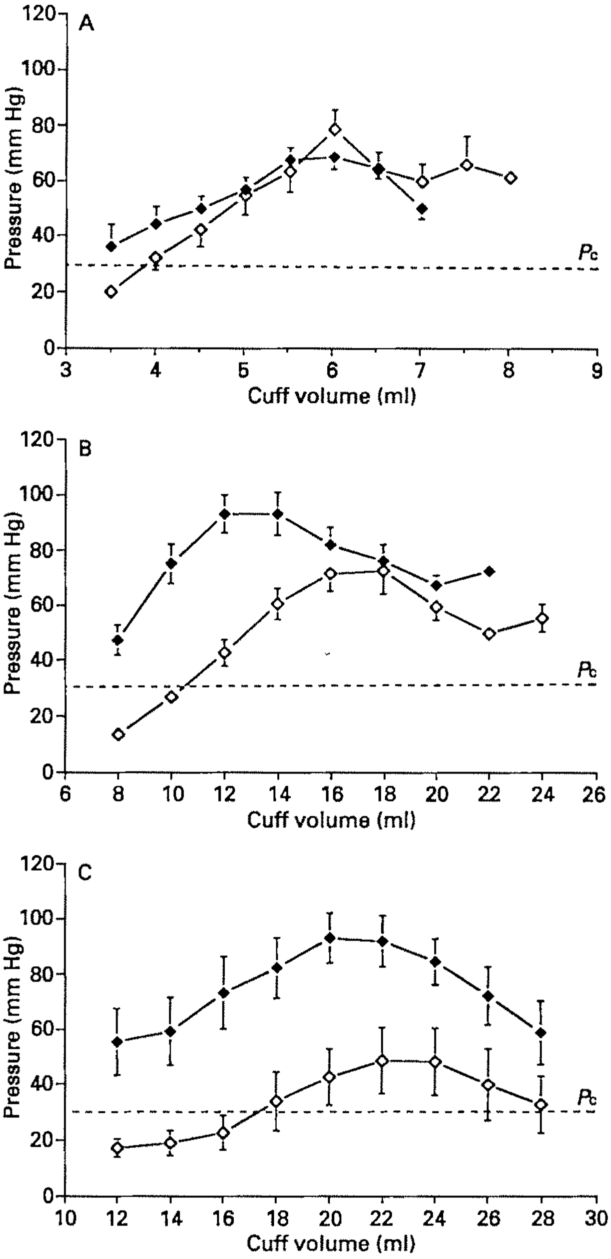


FIG. 3. The calculated pharyngeal mucosal pressures for the start (Ppm_s) (◆) and end (Ppm_e) (◇) of anaesthesia, for (A) size 2, (B) size 3 and (C) size 4 laryngeal mask airways. *Pc* is an estimate of mucosal capillary perfusion pressure.

The disadvantages of this cuff design have been described for tracheal tubes. Grimm and Knight [11] warned that the large intracuff pressure required to expand these cuffs to fill the trachea had the effect that an unknown pressure would be transmitted to the mucosa. Dobrin and Canfield [12] demonstrated that these cuffs, rather than conforming to the trachea, distort it, applying increasing pressure to the mucosa first encountered. McGinnis and colleagues [13] concluded that excessive lateral wall pressure was unavoidable if extensible occluding cuffs were used. This had led to the development of large-volume tracheal tube cuffs, enabling the maintenance of small intracuff pressure and therefore small lateral wall pressures.

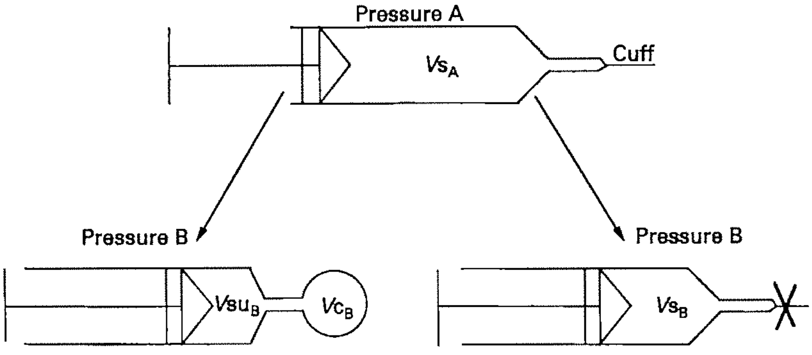


FIG. 4. Method of calculating cuff volume from injected volume.

Nordin [4] suggested that pressure was the principal determinant of cuff-induced tracheal mucosal morbidity, and demonstrated that cuff pressures exceeding 50 mm Hg, exerted upon the rabbit mucosa, resulted in partial denuding of the basement membrane. Seegobin and Van Hasselt [6] assessed fibreoptically the tracheal mucosa underlying the cuff in patients and observed that pressures exceeding 38 mm Hg resulted in total occlusion of mucosal blood flow.

Safe, prolonged tracheal intubation warrants a tracheal cuff that is compliant, deformable and inflated easily to a volume greater than the trachea with maintenance of the intracuff pressure less than 30 mm Hg [14].

For the cuffs of these sizes of LMA, the calculated transmitted lateral wall pressures were substantial when inflated with the recommended injection volumes and likely to exceed the pharnygeal mucosal capillary perfusion pressure (fig. 3).

Two features of the LMA cuff distinguish it from cuffs of tracheal tubes. First, there was not a sustained increase in transmitted lateral wall pressure with increasing cuff volume (fig. 3). Several factors could account for this. A degree of pharyngeal accommodation accompanying incremental cuff inflation might occur. Normally, there is cranial migration of the LMA in the hypopharynx as it is inflated [3], and the large intracuff pressure generated with the LMA *in situ* could result in configurational changes in the cuff, resulting in underestimation of the calculated transmitted pressure. In an evaluation of the methodology used in this study, Black and Seegobin [15] concluded that the derived pressures tended to be underestimates when the cuff became stretched, for this reason. The second distinguishing feature is that the transmitted lateral wall pressure decreased during the time the mask is *in situ* ($P\text{pm}_s$ *vs* $P\text{pm}_e$). Unlike the trachea, the pharynx is a fibromuscular tube which is capable of accommodating an object placed within it, such as an LMA. The apparent reduction in pharyngeal muscular tone with general anaesthesia [16] may also contribute to this decrease in pressure. The sizes 2 and 3 LMA demonstrated this phenomenon only at small cuff volumes. This could reflect a greater mask:pharyngeal size ratio which would limit any effect of pharyngeal accommodation.

An important advantage of the LMA is that insertion and removal do not require visualization of the airway. The incidence and degree of pharyngeal mucosal morbidity, therefore, remains undetermined; there has been one case report of trauma [7]. The incidence of postoperative sore throat with the LMA ranges between 7 and 12% [17–19]. Postoperative "dryness of the throat" was noted in 36% of patients in one study [19]. The aetiology of sore throat after general anaesthesia is multifactorial [20]. It correlates with the surface area of the cuff in contact with the mucosa, and not the lateral wall pressure generated by the cuff [21,22].

Cuff volume and intracuff pressure increased in all patients during anaesthesia. Nitrous oxide was detected in the gas from the cuffs. The gas concentrations recorded could be an underestimation as a result of the small sample volumes obtained for analysis by the Datex Cardiocap analyser. The 9–17.6% increases in cuff volume were less than the increases described previously for a range of tracheal tube cuffs exposed to nitrous oxide, even with consideration for the shorter anaesthetic time [23, 24]. The large intracuff pressure generated with the LMA *in situ* would increase the partial pressure of nitrous oxide within the cuff, decreasing the pressure gradient across the cuff wall, thereby limiting diffusion [23]. In addition, there may be a proportion of the cuff exposed to the air in the patient's upper pharynx, allowing nitrous oxide to diffuse back out of the cuff. Although nitrous oxide diffusion into the cuff increased cuff volume and intracuff pressure, this did not result in an increase in the pressure exerted upon the pharyngeal mucosa (fig. 3).

The site of the transmitted lateral wall pressure cannot be determined here. It is likely to differ in different parts of the pharynx, as the maximum cuff seal around the laryngeal inlet has been found to be only approximately 15 mm Hg [3].

The pharyngeal mucosal pressures demonstrated for the LMA are particularly unwarranted during spontaneous ventilation, as the cuff is not designed to secure the trachea from gastric aspiration, nor is it necessary for it to provide a high-pressure seal around the laryngeal inlet.

The pharyngeal mucosal pressures resulting from the LMA cuff depend, in a complex manner, upon the relative dimensions of the pharynx and LMA, the degree of accommodation by the pharynx and the inflation pressure required to extend the cuff sufficiently for its function as an airway. The morbidity resulting from this transmitted mucosal pressure is undetermined. It may be an important consideration when prolonged or repeated LMA usage is anticipated. Pressure upon the pharyngeal mucosa could be limited by reducing the cuff inflation volumes sufficiently so as not to exceed the residual volumes of the cuff. The intracuff pressure could then be monitored and maintained at a value less than expected mucosal capillary perfusion pressure. Intracuff pressure monitoring is now recommended by the manufacturers "to avoid postoperative throat discomfort" [3], although no guidelines are given as to an acceptable intracuff pressure. Lumb and Wrigley have suggested the fitting of a pressure relief valve to the cuff of the LMA [25]. The substantial reductions in cuff volume required to reduce intracuff pressure to less than expected capillary perfusion pressure may interfere with the function of the LMA with its current cuff design.

APPENDIX

The LMA is supported with the syringe and pressure recording system attached and sealed (fig. 1).

Pressure A = −20 mm Hg vacuum within cuff, pilot tube and syringe at the start.

Vs_A = Volume of air in syringe at pressure A (constant at 40, 26 and 10 ml for sizes 4, 3 and 2 LMA, respectively).

Temperature is assumed constant when comparing the pressure–volume curves P1 with P2, and P3 with P4, as P2 was recorded *immediately* after insertion and P4 *immediately* after removal of the LMA.

Then (fig. 4):

The pilot tube is clamped as it enters the cuff and the system is inflated to pressure B.

Vs_B = volume remaining in the syringe at pressure B.

Then:

The pilot tube is unclamped and the cuff inflated to pressure B.

Vsu_B = volume remaining within the unclamped syringe at pressure B.

Vc_B = cuff volume at pressure B.

Applying the gas law, $\frac{PV}{T}$ = constant.

$$\begin{aligned}\text{Pressure A} \times Vs_A &= \text{pressure B} \times Vs_B \\ &= \text{pressure B} \times Vsu_B + \text{pressure B} \times Vc_B\end{aligned}$$

Therefore:

$$Vc_B = Vs_B - Vsu_B$$

For example: the starting volume in the syringe for the size 4 LMA was 40 ml ($Vs_A = 40$). Injecting 30 ml caused an increase in pressure (pressure B) with a volume of 10 ml remaining in the syringe ($Vsu_B = 10$). Reinflating from the start point with the pilot tube now clamped to pressure B resulted in a volume of 32 ml remaining in the syringe ($Vs_B = 32$). Thus, with an injection volume of 30 ml, the cuff volume achieved was only $32 - 10 = 22$ ml.

This process was repeated to determine the cuff volumes resulting over the range of intracuff pressure achieved. This procedure was performed at the start of each study for the calculations regarding the pressure–volume curves P1 and P2 and repeated again following the removal of the LMA at the end of the study for the calculations regarding the pressure–volume curves P3 and P4.

REFERENCES

1. Brain AIJ. The laryngeal mask—a new concept in airway management. *British Journal of Anaesthesia* 1983; **55**: 801–805.
2. Brain AIJ. Laryngeal mask and trauma to the uvula: a reply. *Anaesthesia* 1989; **44**: 1014–1015
3. Brain AIJ. *The Intavent Laryngeal Mask: Instruction Manual*, 2nd Edn. Windsor: Colgate Medical Limited, 1991.
4. Nordin U. The trachea and cuff induced tracheal injury. An experimental study on causative factors and prevention. *Acta Otolaryngologica* 1976; (Suppl.) **345**: 1–71.
5. Nordin U, Lindholm CE, Wolgast M. Blood flow in the rabbit tracheal mucosa under normal conditions and under the influence of tracheal intubation. *Acta Anaesthesiologica Scandinavica* 1977; **21**: 81–94.
6. Seegobin RD, Van Hasselt GL. Endotracheal cuff pressure and tracheal mucosal blood flow: endoscopic study of effects of four large volume cuffs. *British Medical Journal* 1984; **288**: 965–968.
7. Marjot R. Trauma to the posterior pharyngeal wall caused by a laryngeal mask airway. *Anaesthesia* 1991; **46**: 589–590.
8. Homi J, Notcutt W, Jones JJ, Sparke BR. A method for comparing endotracheal cuffs: A controlled study of tracheal trauma in dogs. *British Journal of Anaesthesia* 1978; **50**: 435–445.
9. Tonnesen AS, Vereen L, Arens JF. Endotracheal tube cuff residual volume and lateral wall pressure in a model trachea. *Anesthesiology* 1981; **55**: 680–683.
10. Carrol RG, McGinnis GE, Grenvik A. Performance characteristics of tracheal cuffs. *International Anesthesiology Clinics* 1974; **12**: 111–131.
11. Grimm JE, Knight RT. An improved intratracheal technic. *Anesthesiology* 1943; **4**: 6–11.
12. Dobrin P, Canfield T. Cuffed endotracheal tubes: mucosal pressures and tracheal wall blood flow. *American Journal of Surgery* 1977; **133**: 562–568.
13. McGinnis GE, Shively JG, Patterson RL, Magovern GJ. An engineering analysis of intratracheal tube cuffs. *Anesthesia and Analgesia* 1971; **50**: 557–564.
14. Lewis FR, Schlobohm RM, Thomas AN. Prevention of complications from prolonged tracheal intubation. *American Journal of Surgery* 1978; **135**: 452–457
15. Black AMS, Seegobin RD. Pressures on endotracheal tube cuffs. *Anaesthesia* 1981; **36**: 498–511.
16. Nandi PR, Charlesworth CH, Taylor SJ, Nunn JF, Doré CJ. Effect of general anaesthesia on the pharynx. *British Journal of Anaesthesia* 1991; **66**: 157–162.
17. Alexander CA, Leach AB. Incidence of sore throats with the laryngeal mask. *Anaesthesia* 1991; **46**: 791.
18. Sarma VJ. The use of a laryngeal mask airway in spontaneously breathing patients. *Acta Anaesthesiologica Scandinavica* 1990; **34**: 669–672.
19. Maltby JR, Loken RG, Watson NC. The laryngeal mask airway: clinical appraisal in 250 patients. *Canadian Journal of Anaesthesia* 1990; **37**: 509–513.
20. Latto IP. *Difficulties in Tracheal Intubation*. East Sussex: Baillière-Tindall, 1985; 66–71.
21. Loeser EA, Machin R, Colley J, Orr D, Bennett G, Stanley TH. Postoperative sore throat—importance of endotracheal tube conformity versus cuff design. *Anesthesiology* 1978; **49**: 430–432.
22. Jensen PJ, Hommelgaard P, Sondergaard P, Eriksen S. Sore throat after operation: influences of tracheal intubation, intracuff pressure and type of cuff. *British Journal of Anaesthesia* 1982; **54**: 453.
23. Stanley TH. Nitrous oxide and pressures and volume of high- and low-pressure endotracheal-tube cuffs in intubated patients. *Anesthesiology* 1975; **42**: 637–640.
24. Revenas B, Lindholm CE. Pressure and volume changes in tracheal tube cuffs during anaesthesia. *Acta Anaesthesiologica Scandinavica* 1976; **20**: 331–326.
25. Lumb AB, Wrigley MW. The effect of nitrous oxide on the laryngeal mask cuff pressure: *in vitro* and *in vivo* studies. *Anaesthesia* 1992; **47**: 320–323.

British Journal of Anaesthesia 1993; **70**: 30–33

COMPARISON OF THE REINFORCED LARYNGEAL MASK AIRWAY AND TRACHEAL INTUBATION FOR ADENOTONSILLECTOMY

P. J. WILLIAMS AND P. M. BAILEY

SUMMARY

*One hundred and four patients were allocated randomly to receive anaesthesia for adenotonsillectomy via either a reinforced laryngeal mask airway or a tracheal tube. Airway maintenance and protection were assessed during and after operation. The reinforced laryngeal mask did not interfere with surgical access; it resisted compression and protected the lower airway from contamination with blood. Four patients were withdrawn from the laryngeal mask airway group: two because of difficulty with placement, and two because the laryngeal mask was obstructed distally when the Boyle Davis gag was opened fully. In children, recovery was less eventful in the laryngeal mask airway group, with less airway obstruction (*P *< 0.001) and better airway acceptance (*P *< 0.05). The reinforced laryngeal mask airway provided a clear, secure airway until recovery of protective reflexes.* (Br. J. Anaesth. 1993; **70**: 30–33)

KEY WORDS

Anaesthesia: otorhinolaryngological. Equipment: laryngeal mask airway.

The laryngeal mask airway is made of silicone but, although the tube portion is relatively stiff, it is compressed or kinked easily and thereby obstructed. A modified laryngeal mask airway has been produced, with a reinforced tube portion which is suitable for use with a Boyle Davies gag, and its use in anaesthesia for adenotonsillectomy was described in 1990 [1].

Anaesthesia for adenotonsillectomy with tracheal intubation may be compromised by tracheal tube compression or displacement [2]. It subjects the patient to the complications of tracheal intubation [3], bronchial intubation with preformed tracheal tubes [4] and aspiration of blood past uncuffed tubes. Extubation at the end of surgery is performed either under deep anaesthesia, leaving an unprotected, insecure airway, or awake, risking excessive coughing and postoperative haemorrhage.

These problems might be avoided by using the modified laryngeal mask airway, as the tube portion is reinforced and resistant to compression and kinking. A correctly positioned laryngeal mask attains a gas-tight seal of up to 2 kPa [5] and has been shown to protect the larynx from dye placed in the pharynx [6].

The aim of this study was to compare the reinforced laryngeal mask airway with tracheal intubation for adenotonsillectomy.

PATIENTS AND METHODS

The study was approved by the Hospital Ethics Committee. Patients of ASA grades I and II, undergoing elective tonsillectomy and or adenoidectomy were allocated randomly (by the toss of a coin) to receive either a reinforced laryngeal mask airway or an RAE preformed orotracheal tube. Patients were not studied if there were any contraindications [5] to the use of a laryngeal mask airway, or if they weighed less than 15 kg. Patients were withdrawn if the quality of anaesthesia jeopardized either the patient or the success of surgery.

Children were premedicated with trimeprazine 2 mg kg^{-1} and atropine 0.02 mg kg^{-1} orally and EMLA cream was applied to the dorsum of both hands 1.5 h before operation. Adults received papaveretum 0.2 mg kg^{-1} i.m. and hyoscine 0.004 mg kg^{-1} 1 h before operation.

Anaesthesia was induced with thiopentone 5 mg kg^{-1} or halothane in 50% nitrous oxide and oxygen. Tracheal intubation was facilitated by administration of suxamethonium 1 mg kg^{-1} i.v. and, in children, the correct tube size was confirmed by demonstration of a small leak with positive pressure ventilation. The laryngeal mask was inserted without the use of a neuromuscular blocker when the patient did not respond to jaw lift, and correct placement was confirmed by the presence of a clinically clear airway and the ability to inflate the patient's lungs manually with no audible gas leak.

Anaesthesia was maintained by spontaneous breathing of 66% nitrous oxide in oxygen and 1–1.5% halothane. Patients were placed supine with a shoulder bar and pillow removed to extend the neck. Monitoring comprised pulse oximetry, capnography, ECG and automated non-invasive arterial pressure.

P. J. WILLIAMS*, B.M., F.R.C.ANAES,; P. M. BAILEY, M.B., B.S., F.R.C.ANAES.; Department of Anaesthesia, The Royal National Throat, Nose & Ear Hospital NHS Trust, Gray's Inn Road, London WC1X 8DA. Accepted for Publication: August 4, 1992.

*Present address, for correspondence: Department of Anaesthesia, Lewisham Hospital, Lewisham High Street, London SE13 6LH.

At the end of surgery, the pharynx was cleared of blood under direct vision and, in the tracheal tube group, the larynx was viewed to detect any blood on the vocal chords. Patients then breathed 100% oxygen with halothane for 3 min, after which an Olympus LE1 fibreoptic bronchoscope was passed down either the laryngeal mask, to inspect the larynx and interior of the mask, or the tracheal tube, to view the trachea. The bronchoscope was not passed beyond the end of the tracheal tube.

All patients were placed in the left lateral position with a pillow under the shoulder during recovery. The laryngeal mask was left *in situ*, while the tracheal tube was removed and a Guedel airway used to aid airway maintenance. All patients were monitored with pulse oximetry and received 40% oxygen until awake.

All anaesthetics were given by the authors and surgery was performed by surgeons of all grades who were familiar with the procedure. Neither the anaesthetist nor the surgeon was randomized.

Data were analysed using Student's t test and χ^2 test for 2×2 contingency tables with Yates' correction.

RESULTS

Patient characteristics and surgical procedure for the two groups are shown in tables I and II. Although the tracheal group appear younger and lighter, the difference is not significant statistically.

One hundred and four patients were recruited, but four patients were withdrawn from the laryngeal mask group (table III): two because of difficulty with laryngeal mask insertion, and two because the laryngeal mask airway became obstructed when the Boyle Davis gag was opened fully. In one of the last two, surgical access was inadequate.

In the remaining patients, surgical access (table IV) was good or adequate, with the laryngeal mask airway being hidden from view when the Boyle Davis gag was opened fully.

There were no episodes of airway obstruction in either group in the remaining patients.

One laryngeal mask airway was displaced by the laryngoscope during pharyngeal toilet at the end of surgery. It was repositioned easily while *in situ* and no aspiration of blood occurred.

Laryngeal spasm occurred in three patients—once on tracheal extubation, which was treated with 100% oxygen; no desaturation occurred. In the laryngeal mask group, insertion of the Boyle Davis gag induced laryngeal spasm in one patient because of inadequate depth of anaesthesia. This was treated by deepening anaesthesia with i.v. thiopentone and manual ventilation; desaturation was prevented. The third episode resulted from accidental laryngeal stimulation during fibreoptic inspection of the inside of the laryngeal mask and larynx. This was the only case of oxygen desaturation (to 75%) during operation and it was treated with i.v. suxamethonium 50 mg and manual ventilation with 100% oxygen via the laryngeal mask.

TABLE I. *Patient characteristics (mean* (SD) *[range])*

	Laryngeal mask airway ($n = 48$)	Tracheal tube ($n = 52$)	P
Age (yr)	11.2	9.3	> 0.1
	[3–31]	[3–37]	
Sex (M/F)	24/24	25/27	
Weight (kg)	39.4 (20.9)	32.3 (18.7)	> 0.05
	[15–90]	[15–88]	

TABLE II. *Surgical procedure*

	Laryngeal mask airway ($n = 48$)	Tracheal tube ($n = 52$)
Tonsillectomy	25	18
Adenotonsillectomy	12	16
Adenoidectomy	1	0
Myringotomy + adenotonsillectomy	7	11
Myringotomy + adenoidectomy	3	4
Submucosal diathermy + adenoidectomy	0	1
Cautery to turbinate + adenotonsillectomy	0	1
Antral washout + adenotonsillectomy	0	1

TABLE III. *Details of four patients withdrawn from laryngeal mask group*

Patient No.	Age (yr)	Weight (kg)	Reason for withdrawal
1	8	32	Inadequate surgical access
2	6	25	Obstructed by Boyle Davis gag
3	3	15	Unsuccessful placement
4	6	23	Unsuccessful placement

TABLE IV. *Peroperative observations.* **Patient is one of the two with laryngeal spasm*

	Laryngeal mask airway ($n = 48$)	Tracheal tube ($n = 52$)	P
Surgical access			
Good	44	51	> 0.1
Adequate	4	1	
Complications			
Obstruction	0	0	
Displacement	1	0	> 0.5
Bronchospasm	0	0	
Laryngeal spasm	2	1	> 0.5
Oxygen desaturation (< 94%)	1*	0	> 0.5

Where there were statistically significant differences between the groups, we have analysed the results according to age because the incidence of perioperative aspiration and postoperative airway obstruction, in particular, varied with age in the tracheal tube group. Aspiration of blood into the lower airway occurred frequently in the intubation group (table V), particularly in children, extending past the carina in three children. However, in the laryngeal mask airway group, there were no cases of aspiration of blood into the larynx ($P < 0.001$) and only one instance when a small amount of blood entered a laryngeal mask. The presence of blood in the lower airway of children (table VI) was associated

TABLE V. *Perioperative observations. Analysis of laryngeal and tracheal contamination*

Blood in larynx	Laryngeal mask airway	Tracheal tube	*P*
Children (< 14 yr)	(*n* = 34)	(*n* = 39)	
None	34	18	< 0.001
Larynx	0	13	
Larynx and trachea	—	5	
Larynx and carina	—	3	
Adults	(*n* = 14)	(*n* = 13)	
None	14	11	> 0.1
Larynx	0	1	
Larynx and trachea	—	1	

TABLE VI. *Perioperative aspiration of blood in the intubation group of children (< 14 yr) and postoperative sequelae*

	Aspiration of blood		
	Yes (*n* = 21)	No (*n* = 18)	*P*
Coughing			
Yes	6	0	< 0.05
No	15	18	
Biting			
Yes	0	1	> 0.5
No	21	17	
Laryngeal spasm			
Yes	3	1	> 0.5
No	18	17	
Desaturation (< 94 %)			
Yes	1	2	> 0.5
No	20	16	

TABLE VII. *Recovery observations in children (< 14 yr). Mandibular support was used when there was partial or complete airway obstruction despite the use of an airway*

	Laryngeal mask airway (*n* = 34)	Guedel airway (*n* = 39)	*P* (95 % CI)
Airway maintenance			
Easy	33	23	< 0.001
Mandibular support	1	16	(0.21–0.54)
Airway acceptance			
Good	33	30	< 0.05 (0.06–0.34)
Coughing	0	6	> 0.05
Biting	0	1	> 0.5
Laryngeal spasm	1	4	> 0.1
Suction			
Easy	30	25	> 0.5
Difficult	1	1	
Not required	3	13	< 0.05 (0.07–0.42)
Desaturation (< 94 %)	0	3	> 0.1
Blood staining			
Outer surface	34		
Inner surface	6		

with an increase in coughing during recovery ($P < 0.05$). There were no cases of perioperative blood loss requiring i.v. fluid replacement (i.e. loss greater than 10 % of calculated blood volume) and no episodes of postoperative haemorrhage.

In children, maintenance of an unobstructed airway during recovery (table VII) was much easier with the laryngeal mask airway than with the Guedel airway ($P < 0.001$) and airway acceptance was better ($P < 0.05$). Suction to clear secretions and blood was easy in both groups, but was required less in the tracheal intubation group ($P < 0.05$). In adults, a similar pattern was observed for airway maintenance and acceptance and the need for suction during recovery, but the number of adults studied was too small to show a statistically significant difference.

Oxygen desaturation to 92 %, 90 % and 88 % occurred in three children in the intubation group; two cases resulted from laryngeal spasm and one from upper airway obstruction. One patient required further surgery to control bleeding detected while the laryngeal mask was still in place. Anaesthesia was deepened and haemostasis achieved.

DISCUSSION

Our results show that the reinforced laryngeal mask airway may be used in place of tracheal intubation during anaesthesia for adenotonsillectomy.

It is noteworthy that the laryngeal mask airway did not obstruct the surgical field and, when the Boyle Davis gag was opened fully, the surgeon could not distinguish between it and a tracheal tube. Adequate, rather than good, surgical access occurred in children in both groups. In addition, the laryngeal mask airway protected the lower airway from aspiration of blood during operation; in contrast, in the intubation group, aspiration of blood occurred in 54 % of children and 15 % of adults.

Although we did not see the trachea in the laryngeal mask group, we have assumed the trachea was not contaminated because there were no cases of laryngeal contamination and only one case of blood entering the laryngeal mask airway by the end of surgery.

Four children had to be withdrawn from the laryngeal mask group, two because the laryngeal mask became obstructed and two because it proved impossible to place the reinforced laryngeal mask correctly. This was caused by very large tonsils causing the mask portion to rotate on the flexible tube of the laryngeal mask airway.

The airway was compromised in three patients in the laryngeal mask group. One patient developed mild laryngeal spasm on insertion of the Boyle Davis gag, and this highlights the need to ensure adequate depth of anaesthesia. In two children with small, narrow, long mouths and restricted mouth opening, the reinforced laryngeal mask airway was obstructed distally when the Boyle Davis gag was opened fully. This was probably a result of the gag pushing the laryngeal mask anteriorly, causing the aperture to be occluded by the epiglottis, which may also have been down-folded. Such cases, when identified, require tracheal intubation, but it must be remembered that occasionally, in patients with severely limited surgical access, the Boyle Davis gag must be inserted asymmetrically to avoid tracheal tube compression, and one tonsil removed before repositioning the gag to remove the other tonsil.

With the exception of the above three patients and the iatrogenic case of laryngeal spasm, the laryngeal mask airway provided as clear an airway as the RAE tube. It is of note that while the Boyle Davis gag is *in situ* the laryngeal mask airway (or the RAE tube) is held firmly in place by the gag and displacement is unlikely to occur.

One laryngeal mask airway was displaced during pharyngeal toilet. This occurred because the laryngoscope blade elevated the tongue base, allowing the laryngeal mask airway to slip up over it. This can be avoided if care is taken to elevate the mask portion of the laryngeal mask airway and the tongue base together.

It is advocated that the laryngeal mask airway be left in place to ensure a clear airway until recovery of protective reflexes [5]. Our results support this view, as only two patients had problems during recovery. One child developed mild laryngeal spasm and required mandibular support, and one adult coughed on the laryngeal mask, without ill effect. This compares with frequent airway obstruction and coughing and occasional laryngeal spasm and oxygen desaturation when a Guedel airway was used to aid airway maintenance. The cause of upper airway obstruction during anaesthesia is complex [7] and the Guedel airway itself has been associated with causing airway obstruction [8]. These problems can be overcome by leaving the laryngeal mask *in situ* for recovery from anaesthesia.

Suction to clear excessive amounts of blood and secretions pooling in the mouth was required more often in the laryngeal mask group, especially in children, and may be necessitated by the laryngeal mask preventing these fluids from being swallowed or aspirated.

On removal, all laryngeal mask airways were blood-stained on their outer surfaces and in masks from eight patients there was blood staining on the inner surface. We cannot know if this occurred while the laryngeal mask airway was still in place, or during its removal. Of these eight patients, only one child developed mild laryngeal spasm and in the others there were no signs of aspiration of blood. In the Guedel airway group, nine patients coughed, five developed laryngospasm and three suffered oxygen desaturation, possibly suggesting laryngeal contamination during recovery.

The reinforced laryngeal mask airway has been used previously for adenotonsillectomy anaesthesia [1], but there was no direct assessment of laryngeal protection. When 10 ml of methylene blue was placed in the oropharynx [6] there were no cases of laryngeal contamination with dye, although the site of surgery was not specified. We have shown that the laryngeal mask airway did protect the larynx from contamination with blood during surgery on the upper airway.

The laryngeal mask airway is contraindicated in non-fasted patients, in whom there is risk of regurgitation of stomach contents, and in patients with low lung compliance [5]. However, patients with these problems rarely present for elective adenotonsillectomy.

REFERENCES

1. Alexander CA. A modified Intravent laryngeal mask for ENT and dental anaesthesia. *Anaesthesia* 1990; **45**: 892–893.
2. Sen AK, Gupta B. Herniation of RAE tube through split Boyle Davis gag. *Anaesthesia and Intensive Care* 1990; **18**: 577–578.
3. Quartararo C, Bishop MJ. Complications of tracheal intubation: prevention and treatment. *Seminars in Anaesthesia* 1990; **9**: 119–127.
4. Black AE, Mackersie AM. Accidental bronchial intubation with RAE tubes. *Anaesthesia* 1991; **46**: 42–43.
5. Brain AIJ. The Intavent laryngeal mask. *Instruction Manual*, 2nd Edn, 1991.
6. John RE, Hill S, Hughes TJ. Airways protection by the laryngeal mask. *Anaesthesia* 1991; **46**: 366–367.
7. Nandi PR, Charlesworth CH, Taylor SJ, Nunn JF, Doré CJ. Effect of general anaesthesia on the pharynx. *British Journal of Anaesthesia* 1991; **66**: 157–162.
8. Marsh AM, Nunn JF, Taylor SJ, Charlesworth CH. Airway obstruction associated with the use of the Guedel airway. *British Journal of Anaesthesia* 1991; **67**: 517–523.

British Journal of Anaesthesia 1993; 70: 34–37

COMPARISON OF ALFENTANIL WITH SUXAMETHONIUM IN FACILITATING NASOTRACHEAL INTUBATION IN DAY-CASE ANAESTHESIA

R. ALCOCK, T. PEACHEY, M. LYNCH AND T. McEWAN

SUMMARY

We have performed a prospective study in 100 adults (ASA I or II) undergoing day-case dental extraction to compare the conditions for intubation and the postoperative sequelae of suxamethonium and alfentanil as adjuncts to propofol. The patients were allocated randomly to two groups comparable in age, sex and weight. Successful intubation was achieved in 100% of the suxamethonium group and 90% of the alfentanil group. Of the patients who received suxamethonium, 74% developed myalgia on the day after surgery, compared with 20% in the alfentanil group ($P < 0.001$). The proportion of patients who developed sore throat was also less in the alfentanil group than in the suxamethonium group ($P < 0.05$). The proportion of patients who complained of nausea in the two groups was not significantly different. We conclude that alfentanil, as an adjunct to propofol to facilitate tracheal intubation, is more acceptable to patients than suxamethonium in anaesthesia for day-case surgery. (Br. J. Anaesth. 1993; **70**: 34–37)

KEY WORDS

Anaesthesia: day-case. Anaesthetics, intravenous: propofol. Analgesics: alfentanil. Intubation tracheal: complications. Neuromuscular relaxants: suxamethonium.

Suxamethonium has several disadvantages: it may cause bradycardia, anaphylactoid reactions, and an increase in serum potassium concentration, and is a trigger agent for malignant hyperpyrexia. Additionally, the use of suxamethonium is associated with postoperative muscle pains in a significant proportion of patients. In most patients these amount to no more than mild stiffness, but occasionally they may be disabling [1]. Myalgia most often affects the neck, shoulder girdle and abdomen, appearing during the first and second days after surgery. It occurs more often in ambulant patients, with women affected more than men [2]. It is rare in children [3] and the elderly [4].

Many methods have been tried to abolish these pains, such as pretreatment with gallamine, vecuronium, midazolam and aspirin. Pretreatment with a non-depolarizing neuromuscular blocker attenuates the fasciculations which herald the onset of relaxation [5]. The degree to which myalgia may be reduced by pretreatment varies [5–7].

An alternative approach to the use of suxamethonium for tracheal intubation is to use propofol, either alone or in combination with lignocaine [8, 9]. In our experience, a standard induction dose of propofol 2.5 mg kg^{-1} provides inadequate muscle relaxation in unpremedicated patients. Therefore, rather than increase the dose of propofol, which has the potential to cause excessive cardiovascular depression, we decided to combine it with the rapidly acting opioid alfentanil in an attempt to produce adequate depth of anaesthesia for tracheal intubation.

PATIENTS AND METHODS

Approval for the study was granted by the Joint Research and Ethics Committee of the Eastman Dental Hospital and informed consent was obtained from all patients. We studied 100 adults presenting for day-case extraction of wisdom teeth under general anaesthesia. All patients were ASA I or II and unpremedicated. Patients were allocated randomly to two groups. In group A, anaesthesia was induced with propofol 2.5 mg kg^{-1} followed by suxamethonium 1 mg kg^{-1} to facilitate tracheal intubation. Group B received alfentanil 10 μg kg^{-1} followed by propofol 2.5 mg kg^{-1}. In both groups, after ventilation of the lungs with 100% oxygen, the trachea was intubated with an uncuffed red rubber nasotracheal tube, and a throat pack inserted. If conditions in group B were such that intubation was not possible, the patients were then given suxamethonium 1 mg kg^{-1} to facilitate intubation. Anaesthesia was maintained with 70% nitrous oxide in oxygen supplemented by a volatile agent (halothane or isoflurane) as indicated clinically. Ventilation was controlled until spontaneous breathing returned. The patients were monitored with an electrocardiogram, a non-invasive arterial pressure monitor and a pulse oximeter.

R. ALCOCK*, F.R.C.ANAES.; T. PEACHEY†, F.R.C.ANAES; M. LYNCH, M.R.C.P., F.R.C.ANAES.; T. McEWAN, F.R.C.ANAES.; Department of Anaesthetics, Eastman Dental Hospital, Grays Inn Road, London WC1. Accepted for Publication: July 23, 1992.
Present addresses:
*Harefield Hospital, Hill End Road, Harefield, Middx UB9 6JH.
†Department of Anaesthetics, Royal Free Hospital, Pond Street, London NW3 2QG.
Correspondence to M.L.

At the end of the procedure, the tracheal tube was removed while the patient was still deeply anaesthetized. Postoperative pain was controlled with a codeine–aspirin combination (Co-codaprin).

The anaesthetist scored the quality of intubating conditions on the following scale: 1 = excellent—blind nasal or jaw relaxed, cords abducted with no movement on passage of the tube; 2 = good—cords abducted, jaw relaxed, some movement on intubation; 3 = poor—cords adducted, difficulty in opening mouth or movement on intubation; 4 = suxamethonium required for successful intubation of the trachea.

A telephone questionnaire was performed on the day after surgery by an anaesthetist who did not know to which group the patient belonged. The patient was questioned for the presence and severity of: aches, pains and muscle stiffness; sore throat; nausea or vomiting. For each, answers were graded as none, slight, moderate or severe. The patient was also invited to report any other problems relating to their operation.

Data were analysed statistically using chi-square with Yates' correction and Fisher's exact test.

RESULTS

Both groups were well matched for age, weight and sex (table I).

Overall, intubation was accomplished in 100% of the patients in group A and intubating conditions were described as good or excellent in all (table II).

TABLE I. *Age, weight and sex distribution (number, or mean (range or SD))*

	Group A (n = 50)	Group B (n = 50)
Sex (M:F)	14:36	16:34
Age (yr)	28.5 (16–69)	26.7 (17–57)
Weight (kg)	64.1 (11.0)	64.1 (12.1)

Intubation was accomplished without suxamethonium in 45 patients (90%) in group B and intubating conditions were described as good or excellent in 43 patients (86%). Although the proportion of successful intubations was less in men (81%), the difference between the sexes was not statistically significant.

In all five patients from group B who received suxamethonium, failure to intubate the trachea when propofol and alfentanil were used was caused by inadequate depth of anaesthesia.

Overall, 37 patients (74%) in group A suffered muscle pains of any severity as opposed to nine patients (20%) in group B ($P < 0.001$) (table III). Of the men, nine (64%) in group A and five (38%) in group B suffered pains of some type (ns). Of the women, 28 (78%) in group A and four (12%) in group B suffered pains ($P < 0.001$).

The frequency of moderate or severe pain was compared with slight or no pain. Twenty-one patients (42%) in group A, compared with three patients (7.0%) in group B suffered moderate or severe pain ($P < 0.001$). Of the men, four (28%) in group A and one (7%) in group B suffered moderate or severe pains ($P = 0.16$). Of the women, 17 (47%) in group A and two (6%) in group B suffered pains ($P = 0.0013$). There was no significant difference between the sexes.

All five patients in group B who received suxamethonium, reported either moderate or severe pain on the day after surgery.

Overall, 41 patients (82%) in group A and 24 patients (53%) in group B complained of sore throat ($P < 0.05$) (table IV). The differences in both men and women between the suxamethonium group and the alfentanil group were significant ($P = 0.033$ and $P = 0.021$, respectively). There was no significant difference between the sexes. There was no significant difference in the reporting of moderate or severe sore throat between the groups.

The number of people reporting nausea of any degree was five (10%) in group A and six (15%) in

TABLE II. *Conditions for intubation in groups A (those who received suxamethonium) and B (those who received alfentanil) (number (%))*

	Group A			Group B		
Intubating conditions	M	F	Total	M	F	Total
Excellent	14 (100)	34 (94)	48 (96)	10 (62)	22 (65)	32 (64)
Good	0 (0)	2 (6)	2 (4)	2 (12.5)	9 (26)	11 (22)
Poor	0 (0)	0 (0)	0 (0)	1 (6.5)	1 (3)	2 (4)
Suxamethonium required	—	—	—	3 (19)	2 (6)	5 (10)

TABLE III. *Number (%) of patients reporting degrees of muscle pains on the day after surgery in groups A (patients who received suxamethonium) and B (those who received alfentanil). The five patients in group B who required suxamethonium have been omitted.*

	Group A			Group B		
Muscle pain	M	F	Total	M	F	Total
None	5 (36)	8 (22)	13 (26)	8 (62)	28 (88)	36 (80)
Slight	5 (36)	11 (31)	16 (32)	4 (31)	2 (6)	6 (13)
Moderate	3 (21)	14 (39)	17 (34)	1 (7)	1 (3)	2 (5)
Severe	1 (7)	3 (8)	4 (8)	0 (0)	1 (3)	1 (2)

TABLE IV. *Number (%) of patients reporting degrees of sore throat on the day after surgery in groups A (patients who received suxamethonium) and B (those who received alfentanil). The five patients in group B who required suxamethonium have been omitted.*

	Group A			Group B		
Sore throat	M	F	Total	M	F	Total
None	2 (14)	7 (19)	9 (18)	7 (54)	14 (44)	21 (47)
Slight	10 (72)	19 (53)	29 (58)	2 (15)	13 (41)	15 (33)
Moderate	1 (7)	8 (22)	9 (18)	3 (23)	4 (12)	7 (16)
Severe	1 (7)	2 (6)	3 (6)	1 (8)	1 (3)	2 (4)

group B (ns). Only two people in each group reported anything other than slight nausea. There was no significant difference between the sexes.

All other problems reported ($n = 28$) related to pain and swelling at the operative site. There was no significant difference between the two groups (15 in group A and 13 in group B).

DISCUSSION

Our overall success rate of 90%, intubating with propofol and alfentanil, compares favourably with the 95% reported by Keaveny and Knell [8] who successfully intubated the trachea of 19 of 20 patients with propofol alone. Mullholland and Carlisle achieved intubation in 73% of a group of 30 patients using propofol supplemented by lignocaine 1.5 mg kg^{-1} [9]. In our study, intubating conditions were good or excellent in 86% of patients, compared with 60% and 67%, respectively, in the above studies.

Muscle pains after suxamethonium may occur in up to 85% of patients [4]. The 74% incidence noted in our study is comparable to the 66% quoted by Churchill-Davidson in his group of 32 outpatients [1]. Although a greater percentage of women than men complained of muscle pains, the difference was not statistically significant. A difference between the sexes has been described by other authors [2]. The proportion of patients who received suxamethonium and developed moderate or severe pains was 42% in our study. We believe this incidence is unacceptable.

The overall reduction in muscle pains on the day after surgery to 20% in the alfentanil group compares favourably with the reductions achieved by other investigators who pretreated patients receiving suxamethonium with other drugs. Bennetts and Khalil [6] observed muscle pains in 68% of their untreated patients. The frequency of muscle pains was reduced, at best, to 28%, by pretreatment with pancuronium 1 mg and, at worst, to 50% by pretreatment with tubocurarine 2.5 mg. Mingus, Herlich and Eisencraft [5] reduced the frequency of pains on the day after surgery from 70% to 45% by pretreating with tubocurarine 0.05 mg kg^{-1}. The use of vecuronium 0.006 mg kg^{-1} or midazolam 0.025 mg kg^{-1} was less effective. McLoughlin, Nesbitt and Howe [7] reduced postoperative myalgia from 57% in their untreated group to 21% using aspirin 600 mg given orally before operation.

The significantly greater frequency of sore throat in the suxamethonium group was an unexpected finding. We had felt that the increased manipulation of the tracheal tube which is sometimes necessary to achieve intubation in the alfentanil group, might make these patients more liable to sore throat. This difference remains unexplained. The overall frequency of sore throat in both groups was large in comparison with other studies of postoperative morbidity [10]. However, we are unaware of any study on postoperative sore throat in day-case patients undergoing dental extraction.

It is interesting to note that the frequency of nausea was not significantly greater in the alfentanil group than in the suxamethonium group, probably because of the short duration of action of alfentanil. No patient required treatment with antiemetic agents.

On the basis of this study, we believe that alfentanil may be an alternative to suxamethonium as an adjunct to propofol in facilitating tracheal intubation. Its use was associated with a significant decrease in postoperative myalgia without an increase in the frequency of other side effects such as sore throat and nausea. We feel that, in combination with propofol, it is suitable for use in young ambulant patients requiring intubation for day-case surgery. However, with the doses used in this study there was a 10% failure rate. To those wishing to attempt this technique, we make the following recommendations: intubation with propofol and alfentanil should not be attempted if the operator is unfamiliar with the technique of nasotracheal intubation of if difficulty in intubation is anticipated; suxamethonium should be available, drawn up into a syringe; following treatment with alfentanil 10 μg kg^{-1}, propofol should be administered in a dose sufficient to cause relaxation of the jaw (in some patients this may exceed the dose of 2.5 mg kg^{-1} used in this study); suxamethonium should be administered if the cords are not visualized at direct laryngoscopy because of muscular resistance, if there is complete adduction of the cords of if there is a prolonged bout of coughing.

REFERENCES

1. Churchill-Davidson HC. Suxamethonium chloride and muscle pains. *British Medical Journal* 1954; 1: 74–75.
2. Cooke M, McClelland R, Sinclair JH, Hayton-Williams DS. Muscle pain after intramuscular suxamethonium chloride. *British Journal of Anaesthesia* 1963; 35: 121–124.
3. Bush GH, Roth F. Muscle pains after suxamethonium in children. *British Journal of Anaesthesia* 1961; 33: 151–153.
4. Foster CA. Muscle pains that follow administration of suxamethonium. *British Medical Journal* 1960; 2: 254–255.
5. Mingus ML, Herlich A, Eisencraft JB. Attenuation of suxamethonium myalgias. *Anaesthesia* 1990; 45: 834–837.
6. Bennetts FE, Khalil KI. Reduction of post-suxamethonium

pain by pretreatment with four non-depolarizing agents. *British Journal of Anaesthesia* 1981; **53**: 531–535.

7. McLoughlin C, Nesbitt GA, Howe JP. Suxamethonium induced myalgia and the effect of pre-operative administration of oral aspirin. *Anaesthesia* 1988; **43**: 565–567.
8. Keaveny JP, Kneel PJ. Intubation under induction doses of propofol. *Anaesthesia* 1988; **43** (Suppl.): 80–81.
9. Mulholland D, Carlisle RJT. Intubation with propofol augmented with intravenous lignocaine. *Anaesthesia* 1991; **46**: 312–313.
10. Cohen MM, Duncan PG, Pope WDB, Wolkenstein C. A survey of 112,000 anaesthetics at one teaching hospital (1975–1983). *Canadian Anaesthetists Society Journal* 1986; **33**: 22–31.

British Journal of Anaesthesia 1993; 70: 38–41

EFFECT OF AGE, GENDER AND ANAESTHETIC TECHNIQUE ON THE PHARMACODYNAMICS OF ATRACURIUM

C. J. R. PARKER, J. M. HUNTER AND S. L. SNOWDON

SUMMARY

We have measured in 38 patients the plasma concentration profile of atracurium and its effect on the electromyographic first response of the train-of-four. One of three techniques was used to supplement anaesthesia with 66% nitrous oxide in oxygen, 0.9% isoflurane (end-tidal), 0.5% halothane (end-tidal) or midazolam 3–10 mg. A four-parameter threshold pharmacodynamic model was fitted to the data in each patient. Compared with a group of patients anaesthetized with an i.v. technique, the steady-state plasma concentration producing 50% block ($C_P^{ss}{}_{50}$) was reduced by halothane, and to a greater extent by isoflurane. The rate constant for exit from the effect compartment (k_{e0}) correlated negatively with age and was greater in female patients, but unaffected by anaesthetic technique. The values of γ, the slope of the concentration–response curve, and of the threshold ($C_P^{ss}{}_0$) were not affected significantly by age, sex or anaesthetic technique. (Br. J. Anaesth. 1993; **70**: 38–41)

KEY WORDS

Age factors. Neuromuscular relaxants: atracurium. Pharmacodynamics.

Volatile anaesthetic agents potentiate the action of the non-depolarizing neuromuscular blocking drugs [1], and isoflurane is more potent than halothane in equivalent MAC multiples *in vivo* [2–4]. The best attempts to analyse this phenomenon have used an effect compartment model; thus tubocurarine was shown to be potentiated by halothane at its site of action, an effect manifest by a dose-dependent decrease in the parameter $C_P^{ss}{}_{50}$, whilst 1.2% halothane (end-tidal) diminished the rate of equilibration of tubocurarine with its site of action [5]. In pharmacodynamic studies, atracurium was shown to be potentiated by 0.75% isoflurane (end-tidal), which produced a decrease of 18% in the ED_{50} [6], and by 0.8% halothane (end-tidal) which, in children, produced a decrease in the ED_{50} from 170 to 130 μg kg^{-1} [7]. The potentiation of atracurium by volatile anaesthetic agents has not been analysed using an effect compartment model.

Previous pharmacodynamic studies of atracurium have failed to reveal an effect of ageing on the infusion requirements for sustained neuromuscular block [8], in contrast with vecuronium, for which advanced age reduces the infusion requirements [9]. The neuromuscular blocking effect of atracurium has been analysed previously with the aid of a standard effect compartment model at the extremes of age [10, 11]; the number of patients was small however, and the results were essentially negative. Similarly, advanced age had little effect on the parameters of the standard pharmacodynamic model for pancuronium and vecuronium [12]. The effect of gender on pharmacodynamics of non-depolarizing neuromuscular blocking drugs has not been studied previously.

We have analysed the action of atracurium on the first response of the train-of-four using the threshold pharmacodynamic model [13], in healthy adult patients and examined the effect of age, gender and anaesthetic technique on the pharmacodynamic model parameters.

PATIENTS AND METHODS

We studied 38 healthy patients undergoing minor surgery requiring the use of neuromuscular block. The study was approved by the Ethics Committee of the Royal Liverpool Hospital and informed consent was obtained from all patients. The patients (table I) were allocated to three groups, which differed only in the technique used to maintain anaesthesia.

Premedication was given as reported previously [14]. Anaesthesia was induced with fentanyl 25–200 μg and thiopentone 250–500 mg. Anaesthesia

TABLE I. *Physical characteristics of the patients in the three groups (mean (range or* SD*))*

	Isoflurane ($n = 14$)	Halothane ($n = 14$)	Midazolam ($n = 10$)
Age (yr)	36.4	39.7	37.3
	(19–65)	(22–54)	(15–57)
Weight (kg)	63.0	67.4	66.8
	(11.3)	(7.8)	(14.2)
Sex (M:F)	7:7	6:8	4:6

C. J. R. PARKER, M.A., M.D., F.R.C.ANAES.; J. M. HUNTER, M.B., F.R.C.ANAES.; S. L. SNOWDON, M.B., CH.B., F.R.C.ANAES.; University Department of Anaesthesia, 4th Floor, Royal Liverpool Hospital, Prescot Street, P.O. Box 147, Liverpool L69 3BX. Accepted for Publication: July 17, 1992.

was maintained with 0.9% isoflurane (end-tidal) and 66% nitrous oxide in oxygen (group I), 0.5% halothane (end-tidal) and 66% nitrous oxide in oxygen (group II) or with no volatile anaesthetic agent but with 66% nitrous oxide in oxygen supplemented with i.v. midazolam 3–10 mg. End-tidal concentrations of volatile anaesthetic agents were monitored using an infra-red absorption monitor (Datex, Normac).

After induction of anaesthesia, train-of-four electromyographic monitoring was commenced using a Medelec MS6. Two i.v. cannulae were sited, one in each arm: one was used for withdrawal of blood samples, the other for administration of atracurium.

Twenty minutes after induction of anaesthesia, when an electromyographic baseline was established and the end-tidal concentration of volatile anaesthetic agent (if used) was stable, atracurium 0.25 mg kg^{-1} was given by constant rate infusion over 10 min. Ventilation was controlled and the trachea intubated when appropriate; end-tidal carbon dioxide partial pressure was maintained in the range 4.0–5.3 kPa (Datex, Capnomac). Pharmacological antagonism of neuromuscular block was not used.

Blood samples (2.5 ml) were taken before and at 1, 2, 4, 6, 8 and 10 min after the start of the infusion, and at 1, 2, 4, 6, 8, 10, 15, 20, 25, 30, 40, 50, 60, 75 and 90 min after the infusion. The heparinized blood samples were immediately acidified and cooled, and plasma was separated promptly. The plasma was frozen rapidly in liquid nitrogen and stored at −20 °C until subsequent analysis for plasma atracurium concentration by HPLC as described previously [14]. The analysis was performed in duplicate with a coefficient of variation between duplicates typically of less than 6% (range 1.6–11.1%).

Data analysis

A threshold pharmacodynamic model was fitted to the data for each patient [13]. This model is characterized by four parameters: the plasma concentration which would, at steady state, produce 50% block ($C_P^{ss}{}_{50}$); the slope of the concentration–response relationship (γ); the rate constant for exit of drug from the effect compartment (k_{eo}); and the steady-state plasma concentration which would just fail to evoke any effect ($C_P^{ss}{}_{\theta}$). A least-squares criterion was used without any attempt to assign different weights to the pharmacodynamic data points.

Comparisons between groups were performed using the Fisher protected LSD test; comparisons between the sexes were made using the Mann–Whitney test. The relationship between pharmacokinetic variables and age was examined by Pearson's correlation coefficient. Where a variable appeared to be affected by more than one explanatory factor, multivariate linear regression was applied; the significance of added regressors was tested using the *F* test.

RESULTS

The pharmacodynamic model parameters are summarized as mean (SD) for each group (table II).

TABLE II. *Mean (SD) values of the pharmacodynamic model parameters for each group. Possible differences between the groups were evaluated using the Fisher LSD test.* ****Significant difference amongst the three groups* (P < *0.005*)

	Isoflurane	Halothane	Midazolam
$C_P^{ss}{}_{50}$***	357	432	524
(ng ml^{-1})	(65)	(82)	(116)
γ	2.38	2.26	2.44
	(0.31)	(0.32)	(0.35)
k_{eo}	0.119	0.119	0.120
(min^{-1})	(0.025)	(0.038)	(0.023)
$C_P^{ss}{}_{\theta}$	160	176	225
(ng ml^{-1})	(40)	(62)	(91)

TABLE III. *Univariate correlation of certain pharmacodynamic model parameters with age, patients in all three groups considered together. The negative correlation of* k_{eo} *with age is highly significant. In view of the difference in* $C_P^{ss}{}_{50}$ *between the groups, the relationship for this parameter was evaluated using multivariate regression (see text) and is not shown here*

Parameter	*r*	d.f.	*P*
γ	−0.300	36	> 0.05
k_{eo} (min^{-1})	−0.507	36	< 0.005
$C_P^{ss}{}_{\theta}$ (ng ml^{-1})	−0.040	36	> 0.1

Effect of anaesthetic technique

$C_P^{ss}{}_{50}$ tended to be greatest in the patients anaesthetized without a volatile anaesthetic agent, and least in the patients anaesthetized with isoflurane; patients anaesthetized with halothane occupied an intermediate position. The difference amongst the groups was statistically significant ($F = 9.93$; 2,35 d.f.; $P < 0.005$).

Application of the Fisher LSD test showed that $C_P^{ss}{}_{50}$ was greater in patients anaesthetized with midazolam than with halothane ($P < 0.05$), and greater in patients anaesthetized with halothane than with isoflurane ($P < 0.05$).

The values of $C_P^{ss}{}_{\theta}$ also tended to be greatest in patients anaesthetized without a volatile anaesthetic agent and least in patients anaesthetized with isoflurane, but the differences between groups were not significant ($F = 2.88$; 2,35 d.f.; $P > 0.05$).

The values of γ and of k_{eo} were not significantly different between the three groups.

Effect of age

The univariate correlation of the values of the parameters γ, k_{eo} and $C_P^{ss}{}_{\theta}$ with age, for all patients, is shown in table III. Whereas the values of γ and $C_P^{ss}{}_{\theta}$ did not correlate significantly with age, there was a strong negative correlation between the values of k_{eo} and age.

The possibility of an effect of age on the values of $C_P^{ss}{}_{50}$ was assessed by multivariate regression, taking account of the effect of anaesthetic technique; age was not a statistically significant regressor ($F = 0.33$; 1,34 d.f.; $P > 0.1$).

Effect of gender

The effect of gender on the value of k_{eo} was examined by multivariate regression (table IV). It

TABLE IV. *The bivariate regression of* k_{eo} *(*min^{-1}*) on age and gender. The intercept is the hypothetical value of* k_{eo} *in a female, aged 0 yr. On average the value of* k_{eo} *is 0.024* min^{-1} *greater in female than male patients, and declines by* 9.9×10^{-4} min^{-1} *per year of increasing age. The values of* F *for the inclusion of each variable in the regression are shown, together with the degrees of freedom of the numerator and denominator, and the associated values of* P. *The correlations of* k_{eo} *with age and gender are both statistically significant*

Variable	Regression coefficient	SE	F	d.f.	*P*
Intercept	0.167	0.120	—	—	—
Age (yr)	-9.9×10^{-4} ($\mathrm{min}^{-1}\ \mathrm{yr}^{-1}$)	3.0×10^{-4}	10.7	1,35	< 0.005
Sex (M = 1; F = 0)	−0.024 (min^{-1})	0.008	8.73	1,35	< 0.01

can be seen that gender had a statistically significant effect; k_{eo} was on average 0.024 min^{-1} greater in female than male subjects. Multivariate regression taking account of age and gender, and two additional parameters to separate the groups, failed to show an effect of anaesthetic technique on k_{eo}.

The possible effect of gender on the value of $C_P^{ss}{}_{50}$ was evaluated by multiple regression, taking into account the effect of anaesthetic technique. The difference between the sexes was not significant ($F = 3.16$; 1,34 d.f.; $P > 0.05$).

When the patients from all three groups were considered together, there was no significant difference between the sexes in the values of γ ($P > 0.1$) or $C_P^{ss}{}_{\theta}$ ($P > 0.1$).

DISCUSSION

The use of an effect compartment model allows definition of the influence of the volatile anaesthetic agents on the action of a non-depolarizing neuromuscular blocking drug; effects on the sensitivity of the site of action may be differentiated from effects on the access of drug to the end-plate. This study is the first to do so for atracurium. Main findings were that atracurium-induced neuromuscular block was potentiated by both halothane and isoflurane (as shown by a reduction in $C_P^{ss}{}_{50}$), and that isoflurane was more potent in this respect in the concentrations used.

The end-tidal concentrations of halothane and isoflurane were chosen to represent 66–70% of 1 MAC (0.74% for halothane [15]; 1.28% for isoflurane [16]). The volatile anaesthetic concentration was not adjusted to take account of the decrease in MAC with age. Physical considerations suggest that equilibration of the volatile anaesthetic agent with the muscle was unlikely to be complete when the atracurium infusion was started. The choice of a 20-min period was pragmatic, but there is evidence, at least for halothane, that potentiation of the effect of non-depolarizing neuromuscular block is largely complete after 10 min [17].

The relative potency of equal MAC multiples of the two agents in reducing $C_P^{ss}{}_{50}$ agrees with the results of previous purely pharmacodynamic work with older non-depolarizing neuromuscular blocking drugs in the human [2–4]. However, a careful study *in vitro* of the guineapig lumbrical has shown that equal MAC multiples of halothane and isoflurane potentiated tubocurarine to a similar extent [18].

The present study has given no support to the view that the different results *in vivo* and *in vitro* might be reconciled by the different effects of the two agents on muscle blood flow. Isoflurane has been reported to increase muscle blood flow [19], and it has been suggested that this might enhance delivery of drugs to the end-plate. The $C_P^{ss}{}_{50}$ defines the steady-state sensitivity of the site of action; access of the drug to the site of action is explicitly modelled by the parameter k_{eo}, which was not affected by the use of a volatile agent. In this respect, the present findings conflict with those of Stanski and colleagues [5], who found that k_{eo} was depressed significantly by 1.0–1.2% halothane (end-tidal), and to a lesser extent by a smaller concentration. The end-tidal concentration of halothane used in our study was at the lower end of the range used by Stanski and colleagues [5], and the effects they noted might have been reproduced here had a greater concentration been used.

The concentrations of volatile anaesthetics used here were smaller than those for which an effect on muscle blood flow was demonstrated by Stevens and others [19], who used 1.2–2.4% isoflurane (end-tidal) for 5 h, or by Eger and others [20], who used 2% halothane (end-tidal). Furthermore, other studies have failed to show an effect of volatile anaesthetic agents on muscle blood flow; thus neither 1.7% halothane (end-tidal) nor 2.6% isoflurane (end-tidal) altered the gastrocnemius muscle blood flow of the dog [21, 22].

The present mean value of k_{eo} (about 0.12 min^{-1}) is similar to the values for other non-depolarizing neuromuscular blocking drugs. Atracurium may undergo spontaneous degradation close to the site of action, and might be expected to have a somewhat greater value of k_{eo} than other drugs; this is not evident in the present results. The rate of spontaneous degradation of atracurium at the end-plate is unknown, but is unlikely to be higher than $k_{\text{non-organ}}$ determined by Fisher and others [23]—about 0.02 min^{-1}. Such a rate would be difficult to detect in the context of an overall value for k_{eo} of 0.12 min^{-1}.

Whereas previous studies have not considered the possible influence of gender, the effect of age on k_{eo} has been assessed previously for atracurium [11] and for vecuronium and pancuronium [12], with negative results. The magnitude of the effect of age on k_{eo} reported here is about 0.001 $\mathrm{min}^{-1}\ \mathrm{yr}^{-1}$, or about 0.03 min^{-1} over three decades. In previous reports, comparisons were made between groups of five or six patients, and for pancuronium a difference between the young and elderly groups rather greater than this was found, which failed to achieve statistical significance. Other groups might have found an effect had they studied a larger number of patients.

It is tempting to relate the influence of age and gender upon k_{eo} to their possible effects upon the circulation. The rate of onset of gallamine-induced neuromuscular block in the dog has been shown to be related directly to muscle blood flow [24]; the present results for k_{eo} might have been obtained, for example, if muscle blood flow declined with advancing age. Such a suggestion must remain speculative, however, because perfusion appeared to have a lesser effect upon recovery [24]. Furthermore, the influence of age and gender upon the microcirculation of the small hand muscles of the human remains unknown.

We have not demonstrated any effect of age, gender or volatile anaesthetic agents on the values of $C_{\mathrm{P}}^{\mathrm{ss}}{}_{\theta}$. Although it shows a tendency to be reduced by the volatile anaesthetic agents, this was not statistically significant; the coefficient of variation of $C_{\mathrm{P}}^{\mathrm{ss}}{}_{\theta}$ in each group was greater than that for $C_{\mathrm{P}}^{\mathrm{ss}}{}_{50}$. It would not be surprising if $C_{\mathrm{P}}^{\mathrm{ss}}{}_{\theta}$ could not be estimated as precisely as $C_{\mathrm{P}}^{\mathrm{ss}}{}_{50}$, which is a median value, whereas $C_{\mathrm{P}}^{\mathrm{ss}}{}_{\theta}$, which represents the steady-state plasma concentration that just fails to block the most sensitive end-plates, reflects the properties of those few end-plates. The relative imprecision of the estimate of $C_{\mathrm{P}}^{\mathrm{ss}}{}_{\theta}$ compared with $C_{\mathrm{P}}^{\mathrm{ss}}{}_{50}$ militates against finding statistically significant effects, should they exist.

The present findings are also negative with regard to the influence of age, gender and anaesthetic agents on γ. The interpretation of this parameter is most difficult; it is also the most sensitive to model specification [14]. It reflects the difference between the steady-state plasma concentrations of atracurium which produce different levels of block, and is thus a function of the dispersion of the sensitivities of the different end-plates within the muscle. It is therefore understandable that it is unaffected by anaesthetic agents, and seems to be independent of age and gender also.

ACKNOWLEDGEMENTS

The equipment required to measure the plasma concentration of atracurium was purchased in part with a grant from the Wellcome Foundation Ltd. We thank Mr A. Dixon for expert technical assistance.

REFERENCES

1. Auer J, Meltzer SJ. The effect of ether inhalation upon the skeletal motor mechanism. *Journal of Pharmacology and Experimental Therapeutics* 1914; 5: 521–522.
2. Miller RD, Eger EI II, Way WL, Stevens WC, Dolan WM. Comparative neuromuscular effects of Forane and halothane alone and in combination with d-tubocurarine in man. *Anesthesiology* 1971; 35: 38–42.
3. Miller RD, Way WL, Dolan WM, Stevens WC, Eger EI II. Comparative neuromuscular effects of pancuronium, gallamine, and succinylcholine during Forane and halothane anaesthesia in man. *Anesthesiology* 1971; 35: 509–514.
4. Miller RD, Way WL, Dolan WM, Stevens WC, Eger EI II. The dependence of pancuronium- and d-tubocurarine-induced neuromuscular blockades on alveolar concentrations of halothane and Forane. *Anesthesiology* 1972; 37: 573–581.
5. Stanski DR, Ham J, Miller RD, Sheiner LB. Pharmacokinetics and pharmacodynamics of d-tubocurarine during nitrous oxide–narcotic and halothane anesthesia in man. *Anesthesiology* 1979; 51: 235–241.
6. Rupp SM, Fahey MR, Miller RD. Neuromuscular and cardiovascular effects of atracurium during nitrous oxide–fentanyl and nitrous oxide–isoflurane anaesthesia. *British Journal of Anaesthesia* 1983; 55: 67S–70S.
7. Brandom BW, Cook RW, Woelfel SK, Rudd GD, Fehr B, Lineberry CG. Atracurium infusion requirements in children during halothane, isoflurane and narcotic anesthesia. *Anesthesia and Analgesia* 1985; 64: 471–476.
8. d'Hollander AA, Luyckx C, Barvais L, De Ville A. Clinical evaluation of atracurium besylate requirement for a stable muscle relaxation during surgery: lack of age-related effects. *Anesthesiology* 1983; 59: 237–240.
9. d'Hollander AA, Massaux F, Nevelsteen M, Agoston S. Age-dependent dose–response relationship of Org NC45 in anaesthetized patients. *British Journal of Anaesthesia* 1982; 54: 653–657.
10. Fisher DM, Claver Canfell P, Spellman MJ, Miller RD. Pharmacokinetics and pharmacodynamics of atracurium in infants and children. *Anesthesiology* 1990; 73: 33–37.
11. Kitts JB, Fisher DM, Claver Canfell P, Spellman MJ, Caldwell JE, Heier T, Fahey MR, Miller RD. Pharmacokinetics and pharmacodynamics of atracurium in the elderly. *Anesthesiology* 1990; 72: 272–275.
12. Rupp SM, Castagnoli KP, Fisher DM, Miller RD. Pancuronium and vecuronium pharmacokinetics and pharmacodynamics in young and elderly patients. *Anesthesiology* 1987; 67: 45–49.
13. Parker CJR, Hunter, JM. A new four-parameter threshold model for the plasma atracurium concentration–response relationship. *British Journal of Anaesthesia* 1992; 68: 548–554.
14. Parker CJR, Hunter JM. Dependence of the neuromuscular blocking effect of atracurium upon its disposition. *British Journal of Anaesthesia* 1992; 68: 555–561.
15. Saidman LJ, Eger EI II. Effect of nitrous oxide and of narcotic premedication on the alveolar concentration of halothane required for anesthesia. *Anesthesiology* 1964; 25: 302–306.
16. Stevens WC, Dolan WM, Gibbons RT, White A, Eger EI II, Miller RD, De Jong RH, Elashoff RM. Minimal alveolar concentration (MAC) of isoflurane with and without nitrous oxide in patients of various ages. *Anesthesiology* 1975; 42: 197–200.
17. Miller RD, Crique M, Eger EI II. Duration of halothane anesthesia and neuromuscular blockade with d-tubocurarine. *Anesthesiology* 1976; 44: 206–210.
18. Waud BE. Decrease in dose requirement of d-tubocurarine by volatile anesthetics. *Anesthesiology* 1979; 51: 298–302.
19. Stevens WC, Cromwell TH, Halsey MJ, Eger EI II, Shakespeare TF, Bahlman SH. The cardiovascular effects of a new inhalation anesthetic, Forane, in human volunteers at constant arterial carbon dioxide concentration. *Anesthesiology* 1971; 35: 8–16.
20. Eger EI II, Smith NT, Stoetling RK, Cullen DJ, Kadis LB, Whitcher CE. Cardiovascular effects of halothane in man. *Anesthesiology* 1970; 32: 396–409.
21. Theye RA. The contributions of individual organ systems to the decrease in whole-body $V\mathrm{o}_2$ with halothane. *Anesthesiology* 1972; 37: 367–372.
22. Theye RA, Michenfelder JD. Individual organ contributions to the decrease in whole-body $V\mathrm{o}_2$ with isoflurane. *Anesthesiology* 1975; 45: 35–40.
23. Fisher DM, Claver-Canfell P, Fahey MR, Rosen JI, Rupp SM, Sheiner LB, Miller RD. Elimination of atracurium in humans: contribution of Hofmann elimination and ester hydrolysis versus organ-based elimination. *Anesthesiology* 1986; 65: 6–12.
24. Goat VA, Yeung ML, Blakeney C, Feldman SA. The effect of blood flow upon the activity of gallamine triethiodide. *British Journal of Anaesthesia* 1976; 48: 69–73.

British Journal of Anaesthesia 1993; 70: 42–46

MIDAZOLAM–ALFENTANIL: AN ANAESTHETIC? AN INVESTIGATION USING THE ISOLATED FOREARM TECHNIQUE

I. F. RUSSELL

SUMMARY

Thirty-two women underwent major gynaecological surgery with a midazolam–alfentanil total i.v. anaesthetic regimen. Adequacy of anaesthesia was assessed using a "pressure, rate, sweating and tears" (PRST) scoring system in conjunction with the isolated forearm technique (IFT). The IFT revealed that 72% of patients responded during surgery, but none had spontaneous, unprompted postoperative recall for the event. Three patients, on prompting, provided evidence of recall. The IFT, while indicating which patients are responsive, cannot be used to predict who will have postoperative recall. Lack of explicit postoperative recall does not indicate unconsciousness during surgery. Twenty patients, asked specifically during surgery to indicate the presence or absence of pain, experienced pain at some time during their surgical procedure. The PRST score could not be used to predict when a patient was awake. This low-dose i.v. anaesthetic technique cannot be recommended for general use. (Br. J. Anaesth. 1993; **70**: 42–46)

KEY WORDS

Anaesthetic techniques: total i.v. anaesthesia. Analgesics: alfentanil. Hypnotics, benzodiazepines: midazolam.

A total i.v. anaesthetic technique based on infusions of midazolam and alfentanil has been described [1]; this was associated both with prolonged recovery and a high dependence on naloxone (90%) to establish spontaneous ventilation after operation. A similar technique using smaller doses did not have these drawbacks [2]. In addition to providing haemodynamic stability, this latter technique was claimed also to provide "protection against awareness".

The authors [2] relied on simple postoperative interviews to detect recall for intraoperative events. When an isolated forearm technique (IFT) is used in conjunction with anaesthesia, it is evident that such interviews create a misleading impression regarding the adequacy of general anaesthesia. Even when minimal anaesthesia is used, patients who are awake during surgery rarely remember this [3–6]. Because midazolam has significant amnesic properties, this may reduce further the reliability of postoperative interviews for detecting memory of intraoperative events. The present study using the IFT was initiated to investigate the incidence of wakefulness (intraoperative awareness) [3, 4] and explicit recall (conscious memory for intraoperative events), together with an assessment of the reliability of conventional monitoring in predicting intraoperative awakening when using a similar midazolam–alfentanil i.v. anaesthetic technique.

PATIENTS AND METHODS

The study was approved by the Hospital's Clinical Trials Committee, and informed consent was obtained from women presenting for major gynaecological surgery. The women were informed that a tape recorder would be played to them during surgery and that they would be interviewed twice in the postoperative period with special reference to their perioperative memories. They were given no information on the contents of the tape.

All patients were premedicated with i.m. midazolam 5–10 mg 1.5 h before operation. The doses of drugs used for induction and maintenance of anaesthesia, together with the increments of alfentanil and propofol used in response to signs of light anaesthesia are shown in table I. The anaesthetic technique was a slight modification of that described by Desiderio, Thorne and Shah [2]. Suxamethonium and atracurium were used in place of vecuronium; patients' lungs were ventilated with an air–oxygen mixture (40% oxygen) instead of 100% oxygen; the maintenance infusions were commenced before rather than after induction; the infusions were continued to within 5 min instead of 15 min of the end of surgery; light anaesthesia was indicated by a modified "pressure, rate, sweating and tears" (PRST) [7] score (table II) in conjunction with the isolated forearm technique [6] instead of 20% increases in arterial pressure or heart rate.

The PRST score was assessed every 2 min throughout surgery. The systolic arterial pressure and heart rate were recorded by a non-invasive pressure monitor (Dinamap 845XT, Critikon, Tampa, Florida). A PRST score greater than 2, a response to command or strong reflex activity of the isolated hand were defined as indicative of light anaesthesia.

Ian F. Russell, M.B., Ch.B., F.R.C.Anaes., B.Med.Biol., Department of Anaesthesia, Hull Royal Infirmary, Hull HU3 2JZ.
Accepted for Publication: August 10, 1992.

TABLE I. *Drug doses and infusion rates used for induction and maintenance of anaesthesia and in response to signs of "light" anaesthesia.* * *"Response" includes a verified response or strong reflex activity of the isolated hand.* † *As indicated by the isolated hand during surgery by direct communication with the patient*

	Midazolam bolus (μg kg^{-1})	Midazolam infusion (μg kg^{-1} h^{-1})	Alfentanil bolus (μg kg^{-1})	Alfentanil infusion (μg kg^{-1} h^{-1})	Propofol bolus (mg)
Induction	200	150	7	60	—
Maintenance	—	150	—	60	—
Increment if PRST > 2	—	—	7	24	—
Increment if response*	—	—	—	—	25–50
Increment if pain present†	—	—	7	24	25–50

TABLE II. *The PRST scoring system, modified from Evans and colleagues* [7]. *The range of possible scores is 0–8*

Index	Condition	Score
Systolic pressure	< Control + 10 %	0
	< Control + 20 %	1
	> Control + 20 %	2
Heart rate	< Control + 10 %	0
	< Control + 20 %	1
	> Control + 20 %	2
Sweating	Nil	0
	Skin moist to touch	1
	Visible beads of sweat	2
Tears	No excess tears in open eye	0
	Excess of tears in open eye	1
	Tears overflow closed eye	2

TABLE III. *An example of the simple questions asked early in the interview to elicit free recall, and the later leading questions used to elicit prompted recall*

Simple questions
I said I would come and ask you some questions:
1. What was the last thing you remember before going to sleep?
2. What was the next thing you remember?
3. Can you remember anything in between?

Leading questions
I said I would play a tape recorder to you during surgery:
1. Do you remember hearing anything?
2. Do you remember hearing anyone talking to you?
3. Do you remember anyone asking you to do anything?
4. Do you remember anyone asking you to do anything with a hand or arm?
5. Do you remember anyone asking you to do anything with your right hand or arm?

Patients' lungs were ventilated with a non-rebreathing circuit at a rate of 10 b.p.m. and a tidal volume of 10 ml kg^{-1}. At the time of the study, capnography was not available.

The prerecorded 1-min, continuous-loop cassette tape used for the IFT contained a 15-s message instructing the patient to open and close the fingers of her right hand. This message was personalized by the inclusion of each patient's preferred first name as follows: "Name, Name. This is Dr Russell speaking. If you can hear me I would like you to open and close the fingers of your right hand, open and close the fingers of your right hand." The tape was started after the patient was connected to the ventilator and was switched off together with the infusions, 5 min from the end of surgery.

Hand movements were categorized as:

Reflex. Movement of the hand or arm which did not conform to the command on the tape.

Unverified response. Any movement of the hand which appeared to conform to the command.

Verified response. An unverified response or persistent reflex type response which was confirmed by direct communication with the patient. Confirmation involved holding the patient's hand and, while raising one of the ear pieces, speaking directly to the patient: "Name, Name, this is Dr Russell speaking. If you can hear me squeeze my fingers".

After a verified response, 20 patients were requested to indicate the presence or absence of pain by appropriately squeezing the investigator's fingers.

After operation, the patients remained in the recovery/extended care area overnight before being transferred to the ward.

The patients were interviewed 1–4 h after operation and again on the third day. The interviews were structured to obtain evidence of dreaming or recall (of the surgical procedure, the taped commands or other spoken commands). The questions posed during the interview (table III), while becoming increasingly leading, did not presuppose any particular answer. At the end of the second interview, patients were asked if they remembered answering these questions before, and if the investigator had been to see them since their operation.

RESULTS

Thirty-three women were investigated (median age 42 yr (range 24–75 yr; upper and lower quartiles 33, 49 yr); median weight 58 kg (range 43–76 kg; upper and lower quartiles 55,64 kg)). One patient was excluded from the final analysis because the conduct of anaesthesia deviated from the design: she had a PRST score greater than 3 which was inadequately treated. This patient responded to command four times, but had no dreams or recall. One other patient received alfentanil 4200 μg (instead of 420 μg) at induction; 12 min later her responses indicated she was awake and in pain; her record has not been excluded.

The surgical procedures included abdominal hysterectomy (22), vaginal hysterectomy (four), other gynaecological laparotomies (five) and pelvic floor repair (one). Median duration of surgery was 60 min (range 28–110 min; upper and lower quartiles 52, 66 min). Two minutes after the induction dose of midazolam, three patients continued to respond to verbal commands and were given propofol to induce

TABLE IV. *Hand responses observed between induction and the end of the surgical procedure, with some relevant comments*

	Responses			
Patient No.	Reflex	Unverified	Verified	Comments
1	1	0	2	Alfentanil 4200 μg administered instead of 420 μg
2	1	0	3	
3	0	0	1	
4	1	1	4	Opening eyes to command before surgery: given propofol
5	2	0	4	Responding before surgery: given propofol
6	2	1	1	No memory of husband's visit in recovery
7	0	0	0	
8	4	1	4	Excluded in final analysis
9	0	0	4	
10	3	2	3	
11	1	0	1	Prompted recall of command
12	3	0	4	
13	0	0	0	
14	1	0	3	
15	1	1	2	
16	2	0	0	Propofol to complete induction
17	0	0	1	
18	0	0	0	
19	0	0	0	Propofol to complete induction; panic and feeling of suffocation during induction
20	3	2	0	
21	1	1	1	Involuntary opening and closing of fingers during postoperative interview
22	1	0	0	
23	0	0	3	Many nonsensical dreams after operation
24	1	0	1	Nightmares after operation; involuntary opening and closing of fingers during postoperative interview
25	2	0	0	
26	2	0	4	Propofol to complete induction; dreaming of home:? when
27	2	0	3	Propofol before surgery
28	3	1	0	
29	0	0	3	Propofol before surgery
30	3	0	1	
31	0	0	1	
32	5	0	3	
33	2	0	1	

TABLE V. *PRST scores in association with the various responses observed during surgery. B = Before surgery started; S = skin incision; D = during surgery*

	Reflex response			Unverified response			Verified response			
PRST score	B	S	D	B	S	D	B	S	D	Total
0	—	2	19	—	—	4	1	6	22	54
1–2	—	2	16	2	1	1	—	5	11	38
>2	—	—	3	—	—	1	3	2	4	13
Total	—	4	38	2	1	6	4	13	37	105

TABLE VI. *PRST scores of 0 and > 0 and whether or not a response occurred, for all the 2-min intervals throughout surgery*

	PRST = 0	PRST > 0
No response	511	286
Reflex response	22	20
Unverified response	3	6
Verified response	29	25

unconsciousness (table IV). After intubation, four patients responded to commands during presurgical preparations. These women all received propofol before surgery started. One of these patients was noted to open her eyes each time her name was used, but as less than 180 s had elapsed since the administration of suxamethonium and no isolating cuff was inflated, there was no movement of the fingers. None of these women had any dreams or recall.

As may be seen from table IV, after induction of anaesthesia only four women completed the procedure without a hand response and 23 of the 32 patients were responsive at some time during "anaesthesia". Table V shows the PRST scores associated with the various responses observed during anaesthesia, and table VI gives an indication of the predictive value of a PRST score of 0. Table VI shows that 48% of the time when a hand response occurred, the PRST score was > 0. When no hand responses occurred, the PRST score was > 0 only 36% of the time (ANOVA, $P < 0.04$). However, 55% of all verified responses occurred with a PRST of 0. The individual patient data in table IV indicate that there was not an excessive contribution to the number of responses from any one patient.

Twenty patients were asked to indicate the presence or absence of pain during surgery. This enquiry was made 39 times and responses indicated comfort on only 10 occasions. All 20 patients experienced pain at some time during surgery.

No patient showed any evidence of recall when interviewed in the recovery room. On the third day, simple questions (table III) appeared to indicate a total lack of recall for events between induction and the time they "awakened" in recovery. However, more detailed leading questions suggested evidence of recall in three women. One was able to paraphrase the instructions given to verify her single response to the taped command. Two other patients were sure they had been asked to do something with their right hand, and while trying unsuccessfully to recall the command, they both demonstrated the appropriate hand movements involuntarily.

Three patients recalled dreaming at some stage. In the recovery room, one patient reported a pleasant dream, either during surgery or immediately after operation, but the other two patients' dreams, reported on the third day, were clearly in the postoperative period. One of these latter patients described a pleasant dream, while the other had two separate nightmares on the second night.

Data were available relating to memory of the early postoperative period for 28 patients. Only four remembered the investigator's recovery room visit (1.5–2 h after surgery).

DISCUSSION

With the exception of different neuromuscular blocking drugs, the modifications to the original anaesthetic technique [2] were intended to increase the doses of midazolam and alfentanil and the sensitivity of clinical monitoring. Consequently, it was disappointing to find that the PRST score lacked any specificity. Individually, or in aggregate, the physiological variables monitored during surgery seemed of little value in predicting the conscious level of patients. Although the greater proportion of responses (48 %) than non-responses (36 %) occurring with a PRST > 0 was significant statistically ($P < 0.04$), this is not clinically useful. Over 51 % of all responses (54 % for verified responses) occurred when the PRST score was zero. Only 13 (8 %) of the responses were associated with a PRST score > 2.

Desiderio, Thorne and Shah [2] administered increments of alfentanil when either arterial pressure or heart rate increased by more than 20 %. The present study using the modified PRST score was intended to enable earlier intervention by allowing supplements of alfentanil with arterial pressure or heart rate increases of only 10 % in association with other signs of light anaesthesia. In reality, sweating and lachrymation were uncommon (except for lachrymation immediately after intubation or when the patient breathed against the ventilator as the effect of the suxamethonium decreased), while arterial pressure and heart rate did not always increase simultaneously. As a result, 20 % increases in arterial pressure or heart rate, occurring in isolation, did not trigger an alfentanil increment. PRST scores of 2 (equivalent to an increase in arterial pressure or heart rate > 20 %), resulting from only one variable, were achieved in 14 patients (two, sweating; one, tears; eight, heart rate changes; three, arterial pressure changes).

It could be argued that these 14 patients exhibited clear clinical signs of light anaesthesia which was treated inadequately and that this was the reason for the high incidence of intraoperative wakefulness. All three patients with evidence of postoperative recall were included in this group. Conversely, only 10 of the 24 patients who responded to intraoperative commands were in this category and, of these, only one responded during this period. Only five of the 22 patients with reflex actions of the isolated hand had a reflex movement at this time.

The first verified response occurred in association with the skin incision on 13 occasions. Assessing "light anaesthesia" at this time was particularly difficult: lachrymation associated with intubation had ceased; arterial pressure and heart rate were either less than normal or were returning quickly to normal after a hypertensive response to intubation. As the effects of the suxamethonium wore off and patients began to make swallowing movements or breathed against the ventilator, it was not unusual for lachrymation to recommence and for arterial pressure, heart rate, or both, to increase. Inflating the tourniquet and administering atracurium abolished all these clinical signs of "light anaesthesia", thus conveying the clinical impression of "adequate anaesthesia". While neither atracurium [8] nor tubocurarine [9] appear to affect cerebration in conscious volunteers, pancuronium [10] is known to reduce the MAC value for halothane. The cause of this is speculative, and both central and peripheral mechanisms are proposed [10]. Perhaps the most plausible is the suggestion that, by abolishing muscle spindle afferent input to the reticular activating system, neuromuscular blockers promote cortical deafferentation; the result of this is that a given concentration of anaesthetic appears more potent. Thus it may be that, by whatever means, neuromuscular blocking drugs do reduce the dose requirements for "true" anaesthetic drugs and, dose for dose, anaesthesia may be "deeper" in the presence of muscle relaxation.

The limitations of conventional monitoring in predicting intraoperative awareness, as seen in this and other studies [5, 6], indicate that considerable caution should be exercised when interpreting the results of studies suggesting evidence for postoperative recall of information presented during "adequate anaesthesia". In the presence of neuromuscular block and in the absence of the IFT, it may not be possible to ensure that a patient is unconscious when the information is presented. In the present study all three women with postoperative evidence of recall responded to the command during "adequate anaesthesia". Likewise, all three dreaming patients responded during surgery.

The results indicate that, on their own or in combination as the PRST score, the clinical criteria used to assess "depth" of anaesthesia are unreliable and could not be relied on to predict the presence or absence of consciousness during anaesthesia. When using this anaesthetic without the IFT, it is impossible for the anaesthetist to know whether or not a patient is awake.

If the aim of general anaesthesia is to ensure that a patient has no recognizable conscious recall of surgery and views the perioperative period as a "positive" experience then, as suggested [2], this midazolam–alfentanil infusion regimen may fulfil that requirement. However, the definition of general anaesthesia would normally include unconsciousness and freedom from pain during surgery—factors not guaranteed by this technique. In the majority of patients in the present study, the state of mind produced by this low dose midazolam–alfentanil regimen could not be viewed as "general anaesthesia", but rather it should be regarded as "general amnesia".

REFERENCES

1. Vuyk J, Hennis PJ, Burm AGL, de Voogt JWH, Speirdijk J. Comparison of midazolam and propofol with alfentanil for total intravenous anesthesia. *Anesthesia and Analgesia* 1990; 71: 645–650.
2. Desiderio DP, Thorne A, Shah NK. Alfentanil–midazolam anaesthesia: protection against awareness. In: Bonke B, Fitch W, Millar K, eds. *Memory and Awareness in Anaesthesia.* Amsterdam: Swets & Zeitlinger, 1990; 281–285.
3. Tunstall ME. Detecting wakefulness during general anaesthesia for Caesarean section. *British Medical Journal* 1977; 1: 1321.
4. Tunstall ME. The reduction of amnesic wakefulness during Caesarean section. *Anaesthesia* 1979; 34: 316–319.
5. Russell IF. Comparison of wakefulness with two anaesthetic regimens. Total i.v. *v.* balanced anaesthesia. *British Journal of Anaesthesia* 1986; 58: 965–968.
6. Russell IF. Conscious awareness during general anaesthesia: relevance of autonomic signs and isolated arm movements as guides to depth of anaesthesia. In: Jones JG, ed. *Depth of Anaesthesia, Bailliere's Clinical Anaesthesiology,* Vol. 3. London: Baillière–Tindall, 1989; 511–532.
7. Evans JM, Fraser A, Wise CC, Davies WL. Computer controlled anaesthesia. In: Prakash O, ed. *Computing in Anaesthesia and Intensive Care.* Boston: Martinus Nijhoff, 1983; 279–291.
8. Wang M, Russell IF, Charlton PF, Conlon JB. An experimental simulation of anaesthetic awareness and validation of the isolated forearm technique. In: Sebel PS, Winograd E, Bonke B, eds. *Memory and Awareness in Anaesthesia.* Simon and Schuster, 1992; (in Press).
9. Smith SM, Brown HO, Toman JEP, Goodman LS. The lack of cerebral effects of d-tubocurarine. *Anesthesiology* 1947; 8: 1–14.
10. Forbes AR, Cohen NH, Eger EI II. Pancuronium reduces halothane requirement in man. *Anesthesia and Analgesia* 1979; 58: 497–499.

British Journal of Anaesthesia 1993; 70: 47–53

EFFECTS OF ETOMIDATE ON THE ADRENOCORTICAL AND METABOLIC ADAPTATION OF THE NEONATE

T. A. CROZIER, C. FLAMM, C. P. SPEER, W. RATH, W. WUTTKE, W. KUHN AND D. KETTLER

SUMMARY

The effects of etomidate on corticosteroid synthesis were compared with those of methohexitone. We studied 40 neonates, 22 delivered by elective and 18 by emergency Caesarean section. Apgar scores, blood sugar and plasma concentrations of cortisol and etomidate were evaluated at birth and 2 and 6 h postpartum. There was no difference in Apgar scores attributable to the induction agent. The median cortisol concentrations in cord blood were small (136 nmol litre^{-1}; range 47–478 nmol litre^{-1}, and 259 nmol litre^{-1}; range 58–1504 nmol litre^{-1} after elective and emergency sections, respectively). During the study, cortisol concentrations increased in the infants in the methohexitone groups and decreased in those in the etomidate groups; this effect was most evident 2 h after delivery (methohexitone groups 245 nmol litre^{-1}, range 70–959 nmol litre^{-1}; etomidate groups 121 nmol litre^{-1}, range 56–320 nmol litre^{-1}). There was no difference at 6 h postpartum (methohexitone groups 183 nmol litre^{-1}, range 25–756 nmol litre^{-1}; etomidate groups 190 nmol litre^{-1}, range 33–628 nmol litre^{-1}). The concentration changes during the study period differed significantly ($P <$ *0.005) with respect to the induction agent. Blood glucose concentrations were small (mean (SD) in all 40 neonates 2 h postpartum was 2.64 (0.77) mmol litre^{-1}), and did not differ between the groups. There were 17 cases of moderate to severe hypoglycaemia (blood glucose concentrations less than 2.5 mmol litre^{-1}): nine in the etomidate group and eight in the methohexitone group. Mean (SD) fetal: maternal etomidate concentration ratio was 0.48 (0.27) with an umbilical arterial etomidate concentration of 83 (39) ng ml^{-1} (340 (160) nmol litre^{-1}). The concentration was 9.3 (42) ng ml^{-1} (38.0 (22) nmol litre^{-1}) at 2 h and 6 (2.9) ng ml^{-1} (24.6–15 nmol litre^{-1}) at 6 h.* (Br. J. Anaesth. 1993; **70**: 47–53)

KEY WORDS

Anaesthesia: obstetric. Anaesthetics, intravenous: etomidate, methohexitone. Hormones: corticosteroid synthesis. Metabolism: neonatal.

In Western Europe and North America an increasing percentage of newborn children are delivered by Caesarean section and the immediate postpartum condition of the neonate is influenced by the anaesthetic induction agent [1]. The drugs used most commonly are the barbiturates, methohexitone and thiopentone, both of which have similar effects on the neonate [2]. The less frequently used induction agent, etomidate, compares favourably with thiopentone with regard to Apgar scores and the time to sustained spontaneous ventrilation [3].

Etomidate is therefore an alternative induction agent for those patients for whom barbiturates are undesirable (e.g. those with asthma, porphyria, allergy, heart disease). However, etomidate inhibits cortisol synthesis in the adrenal cortex of adults [4, 5], and whilst this probably applies also to neonates, the available data are scarce [6]. Cortisol, glucagon and catecholamines are required for adaptation to extrauterine life in order to maintain a continuous supply of glucose by gluconeogenesis and glycolysis. The circulating plasma concentrations of cortisol are typically smaller in infants delivered by elective Caesarean section than in those after vaginal delivery [7, 8], and a further reduction of cortisol synthesis might therefore impair the adaptive capacity of the infant and lead to an increased incidence of hypoglycaemia [9].

This study was conducted to determine to what extent etomidate, given to the mother for induction of anaesthesia for Caesarean section, affected concentrations of plasma cortisol and blood glucose in the neonate.

PATIENTS AND METHODS

We studied 40 neonates delivered by Caesarean section under general anaesthesia. The study was approved by the Human Ethics Commission of the Medical Faculty of the University of Göttingen, and informed consent was obtained from the mothers. All patients were monitored during the final hours of

---

THOMAS A. CROZIER*, M.D., PH.D., CHRISTIAN FLAMM, M.D., DIETRICH KETTLER, M.D. (Department of Anaesthesiology); CHRISTIAN P. SPEER, M.D. (Department of Paediatrics); WERNER RATH, PH.D., WALTHER KUHN, M.D. (Department of Gynaecology and Obstetrics); WOLFGANG WUTTKE, M.D. (Department of Clinical Endocrinology and Reproduction Biology); University of Göttingen, Federal Republic of Germany. Accepted for Publication: August 12, 1992.

*Address for correspondence: Zentrum Anaesthesiologie, Rettungs- und Intensivmedizin, Robert-Koch Str. 40, 3400 Göttingen, Federal Republic of Germany.

pregnancy by continuous cardiotocography. One group consisted of 22 parturients undergoing elective Caesarean section because of abnormal fetal presentation, previous Caesarean section or documented placenta praevia. None of these patients was in labour, and none had cardiotocographic signs of fetal distress. In the second group there were 18 parturients in labour in whom Caesarean section was performed as an emergency measure because of signs of severe intrauterine fetal distress, such as pathological heart rate deceleration patterns. In each of the two groups the parturients were allocated randomly to receive either methohexitone or etomidate for induction of anaesthesia. Exclusion criteria were diabetes mellitus, eclampsia, recent corticosteroid treatment and known allergy to either etomidate or methohexitone.

Patients were placed on the operating table in a head-up, left lateral position. While the patient was being prepared for surgery, indwelling cannulae were placed in peripheral veins, 500 ml of balanced salt solution was infused i.v., precordial ECG leads were attached and the patient's lungs were preoxygenated for at least 5 min with 100 % oxygen via a face mask. When the obstetricians were prepared for incision, pancuronium 1–1.5 mg was injected i.v. [10, 11] and, as soon as the patient noticed an effect, anaesthesia was induced with a rapid sequence technique using either methohexitone 1 mg kg^{-1} or etomidate 0.4 mg kg^{-1}, followed immediately by suxamethonium 1.5 mg kg^{-1}. Cricoid pressure was applied as soon as the patient lost consciousness and the trachea was intubated within 30 s in all patients. The operation began immediately after the tracheal tube was positioned correctly. The lungs were ventilated with 50 % nitrous oxide in oxygen until the uterus was incised, at which time the gas mixture was changed to 100 % oxygen. Volatile anaesthetics were not added until the umbilical cord was severed, as routine incision-to-delivery time is very short in our institution (< 5 min). After the umbilical cord was clamped, the rest of the operative procedure was conducted under balanced anaesthesia with fentanyl 0.1–0.2 mg, 66 % nitrous oxide and 0.5–1.5 % halothane in oxygen, with pancuronium if necessary. Routine intraoperative monitoring consisted of continuous ECG and arterial pressure, pulse oximetry and capnometry.

The neonates were placed under a radiation heater and cared for by a paediatrician who also performed the Apgar scoring, but who was unaware of the induction drug. The infants were then transferred either to the nursery ward, or to the paediatric intensive care unit if they were markedly distressed or had a birth weight less than 2.5 kg. In our institution, Caesarean section neonates are normally not fed until 6 h postpartum. However, if the results of the first blood sugar determination at 2 h postpartum revealed a value < 1.4 mmol $litre^{-1}$ (25 mg dl^{-1}), the children were fed a small amount of sweetened tea.

Blood samples for cortisol and etomidate were obtained in EDTA-coated tubes, centrifuged immediately, and the plasma was stored at –80 °C until required for assay. Maternal venous samples were taken from the arm contralateral to that used for drug administration before induction of anaesthesia, simultaneously with umbilical cord clamping, and 2 and 6 h postpartum. The initial neonatal sample was obtained from the umbilical artery. The samples at 2 and 6 h postpartum were capillary samples from the heel. Blood sugar measurements at 2 and 6 h postpartum were performed by the hospital laboratory using an automated analyser.

Cortisol measurements were performed in duplicate with a commercially available radioimmunoassay kit (Labordiagnostika Gödecke, Freiburg, West Germany). The antibody is highly specific with a cross-reactivity of only 3.4 % with 11-deoxycortisol and less than 1 % with other steroid hormones. The sensitivity of the assay is 5.5 nmol $litre^{-1}$ (0.2 μg dl^{-1}) with an intra-assay coefficient of variation of 2.2 %. Normal (SD) morning values in our laboratory for adults are 417 (111) nmol $litre^{-1}$ (15 (4) μg dl^{-1}).

Etomidate concentrations were measured by gas chromatography using nitrogen detection with the method described by De Baer, Smeekens and Breimer [12]. The assay has a limit of sensitivity of 2.5 ng ml^{-1} (10 nmol $litre^{-1}$), and coefficients of variation of 6 % at a concentration of 244 ng ml^{-1} (1000 nmol $litre^{-1}$) and 11 % at a concentration of 24.4 ng ml^{-1} (100 nmol $litre^{-1}$).

Statistical analysis

The following hypotheses regarding circulating concentrations of cortisol and glucose were tested: greater plasma concentrations of cortisol are found in neonates delivered by emergency Caesarean section compared with those delivered by elective section; neonatal plasma cortisol concentrations are reduced by etomidate compared with methohexitone; postpartum blood glucose concentrations are smaller in neonates exposed to etomidate than those exposed to methohexitone; etomidate decreases maternal plasma cortisol concentrations. No assumptions were made as to the distribution of the cortisol concentration data in the population of neonates investigated, and they were therefore analysed by the non-parametric Mann–Whitney *U* test or the Kruskal–Wallis test. Confidence intervals for the differences between medians were calculated by the method described by Moses [13]. Blood glucose concentrations were found to be normally distributed, and these data and the patient data were analysed by ANOVA.

RESULTS

There was no significant difference between the groups in maternal age or weight, gestational age, incision to delivery time, amount of etomidate administered or duration of surgery. There was no difference in the induction agent subgroups in birth weight or Apgar score. However, although the gestational age was the same in all groups, the neonates in the emergency Caesarean section group had smaller birth weights and their 1- and 5-min Apgar scores were less than those in the elective Caesarean group (tables I, II).

TABLE I. *Maternal characteristics (means (SE) [range]). No statistically significant differences between Caesarean section groups (group 1 = elective; group 2 = emergency) or between drugs within those groups*

	Group I		Group 2	
	Etomidate	Methohexitone	Etomidate	Methohexitone
Number	11	11	9	9
Age (yr)	27	29	31	29
	[18–36]	[22–39]	[24–40]	[24–35]
Weight (kg)	75 (4.7)	75 (2.3)	71 (3.2)	73 (3.1)
	[56–115]	[67–89]	[56–90]	[62–88]
Duration of op. (min)	52.3 (3.7)	52.3 (2.4)	58.6 (2.2)	54.4 (2.9)
	[28–75]	[45–68]	[48–70]	[45–70]
Etomidate (mg)	24 (1.6)	—	27 (0.8)	—
	[17–34]	—	[24–30]	—

TABLE II. *Neonatal characteristics (mean (SE [range]).* P *values < 0.05 were considered significant. No significant differences between drugs within group 1 and group 2. I–D = incision to delivery*

	Group 1		Group		
	Etomidate	Methohexitone	Etomidate	Methohexitone	*P* (group 1 *vs* group 2)
Number	11	11	9	9	
Gestational age (weeks)	38.8 (0.4)	38.6 (0.6)	39.3 (0.7)	38.3 (0.5)	ns
	[37–41]	[35–41]	[36–42]	[36–41]	
Birth weight (g)	3306 (118)	3552 (174)	3026 (231)	2517 (197)	< 0.01
	[2700–3900]	[2660–4450]	[2120–4035]	[1950–3510]	
I–D time (min)	4.7 (0.3)	4.4 (0.3)	4.2 (0.3)	4.6 (0.3)	ns
	[3–7]	[3–6]	[3–5]	[3–6]	
Apgar score					
1 min	9.3 (0.3)	9.5 (0.2)	8.7 (0.3)	8.6 (0.2)	< 0.01
	[7–10]	[9–10]	[7–10]	[8–10]	
5 min	10 (0)	10 (0)	9.8 (0.2)	9.6 (0.2)	< 0.05
	[10]	[10]	[8–10]	[8–10]	
10 min	10 (0)	10 (0)	9.8 (0.2)	9.9 (0.1)	ns
	[10]	[10]	[8–10]	[9–10]	

TABLE III. *Neonatal cortisol data (median [range] (95% confidence limits for difference between medians)). Group 1 = Elective Caesarean section; group 2 = emergency section. The reduction in plasma cortisol concentrations attributable to the effects of etomidate was significant at* P *< 0.05*

	Cortisol concentration (nmol litre^{-1})						
	Group 1				Group 2		
Sample	Etomidate	Methohexitone	Section		Etomidate	Methohexitone	Section
Umbilical artery	—	—	136 [47–478]		—	—	259 [58–1504]
95% CL				(−19 to 195)			
2 h postpartum	111 [56–320]	214 [70–556]	—		128 [89–192]	295* [81–959]	—
95% CL	(−19 to 292)				(3 to 498)		
6 h postpartum	97 [33–261]	131 [25–756]	—		247 [47–628]	336 [33–556]	—
95% CL	(−67 to 275)				(−158 to 250)		

Plasma cortisol concentrations

The plasma cortisol concentrations in the neonates delivered by elective Caesarean section were in the low normal range, and the median cortisol concentrations in the cord blood of infants delivered by emergency Caesarean section were slightly greater (table III). The median plasma cortisol concentration over the entire 6-h study period was significantly greater ($P < 0.05$) in neonates delivered by emergency Caesarean section (189 nmol litre^{-1}, range 33–1504 nmol litre^{-1}) than in those after elective section (130 nmol litre^{-1}, range 25–756 nmol litre^{-1}).

During the postpartum observation period, median cortisol concentrations in the neonates exposed to etomidate decreased, whereas those in the infants in the methohexitone groups increased. This effect was most obvious at 2 h postpartum. The median change in plasma cortisol concentrations during the entire 6-h study period was an increase in the methohexitone groups of 58 nmol litre^{-1} (range −250 to 617), and a decrease in the etomidate groups of 56 nmol litre^{-1} (range −1415 to 570) ($P < 0.005$).

TABLE IV. *Median [range] maternal plasma cortisol concentrations and † 95% confidence limits for the difference between drug medians (methohexitone – etomidate). Group 1 = Elective Caesarean section; group 2 = emergency section. The reduction in plasma cortisol concentrations at 2 h postpartum attributable to the effects of etomidate was statistically significant* (P = 0.005).

	Cortisol concentration (nmol litre^{-1})		
Sample	Group 1	Group 2	Groups 1 and 2
Before induction or drugs	1156 [489–1473]	1286 [639–2085]	1204 [489–2085]
Umbilical clamping (before drugs)	1172 [639–2029]	1426 [915–1946]	1312 [639–2029]
Etomidate groups	1000 (639–1446)	1418 (1029–1918)	1164 [639–1918]
Methohexitone groups	1361 (945–2029)	1446 (917–1946)	1376 [917–2029]
95% CL†			(–40 to 430)
2 h postpartum			
Etomidate groups	695 (278–945)	695 (361–1835)	699 [278–1835]
Methohexitone groups	1307 (612–2029)	1612 (695–1863)	1368 [612–2029]
95% CL†			(300 to 865)
6 h postpartum			
Etomidate groups	806 (473–1502)	500 (361–1362)	669 [361–1502]
Methohexitone groups	1056 (389–2029)	639 (334–945)	817 [335–2029]
95% CL†			(–240 to 330)

TABLE V. *Mean ((SD) [range]) neonatal blood glucose concentrations and incidence of hypoglycaemia (No.). No statistically significant differences between groups*

	Group 1		Group 2	
	Etomidate	Methohexitone	Etomidate	Methohexitone
Blood glucose (mmol litre^{-1})				
2 h post partum	2.31 (0.92) [1.12–3.64]	2.78 (0.94) [0.9–4.48]	2.65 (0.69) [1.4–3.7]	2.47 (0.86) [1.12–3.53]
6 h postpartum	2.58 (0.53) [1.79–3.08]	3.04 (0.95) [1.68–4.54]	2.73 (0.60) [1.9–3.86]	2.55 (0.37) [1.96–3.14]
Neonates with hypoglycaemia				
Severe (glucose < 1.4 mmol litre^{-1})	4 of 11	1 of 11	1 of 9	2 of 9
Moderate (glucose 1.4–2.5 mmol litre^{-1})	1 of 11	3 of 11	3 of 9	2 of 9
Clinical signs	3 of 11	3 of 11	1 of 9	2 of 9

The 95% confidence limits for the difference show that the median cortisol concentration in the etomidate groups was 61–267 nmol litre^{-1} less than the median in the methohexitone groups.

All parturients had increased preoperative plasma cortisol concentrations which had not changed appreciably at the time of umbilical clamping (table IV). The median plasma cortisol concentration in the methohexitone group was 1376 nmol litre^{-1} (range 917–2029 nmol litre^{-1}) and in the etomidate group 1164 nmol litre^{-1} (range 639–1918 nmol litre^{-1}). At 2 h postpartum (approximately 1 h after the end of surgery) plasma cortisol concentrations in the methohexitone groups had not changed significantly (median change from the time of umbilical clamping, –33 nmol litre^{-1} (range –809 to 562 nmol litre^{-1})), whereas plasma cortisol concentrations in the etomidate groups exhibited a median decrease of 474 nmol litre^{-1} (range –920 to –42). The median concentration in the etomidate groups was 300–865 nmol litre^{-1} smaller than that in the methohexitone groups (95% confidence limits) ($P < 0.005$). There was no difference between the groups at 6 h postpartum (table IV), at which time the median cortisol concentration in the methohexitone groups was 817 nmol litre^{-1} (range 334–2029 nmol litre^{-1}) and that in the etomidate groups 669 nmol litre^{-1} (range 361–1502 nmol litre^{-1}).

Neonatal blood glucose

Mean blood glucose concentrations were in the low normal range of approximately 2.6–2.7 mmol litre^{-1}. The smallest individual blood glucose concentrations were found in neonates in the methohexitone groups. There was no significant differences between the blood glucose concentrations in the four groups at any time and there were no significant changes in blood glucose concentrations during the study (table V). Mean (SD) blood glucose concentration was 2.72 (0.82) mmol litre^{-1} for the 20 neonates in the methohexitone groups and 2.55 (0.77) mmol litre^{-1} for those in the etomidate groups.

In our institution a neonatal blood glucose concentration < 1.4 mmol litre^{-1} is defined as severe hypoglycaemia requiring glucose. Moderate hypoglycaemia with concentrations between 1.4 and 2.5 mmol litre^{-1} is regarded as a transient phenomenon which only requires close monitoring. At 2 h postpartum, nine of 20 neonates exposed to etomidate had developed hypoglycaemia; five cases were classified as severe. Compared with this, eight of the 20 infants delivered by Caesarean section induced with methohexitone developed hypoglycaemia, three severe. The 95% confidence limits for the difference between the means of the two groups show that the blood glucose concentrations could be 0.349 mmol

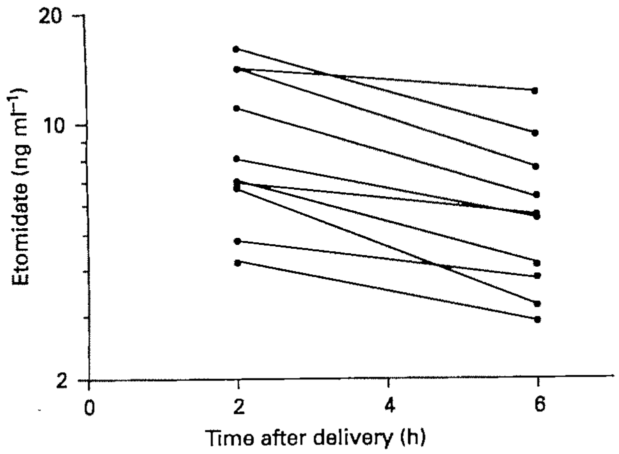


FIG. 1. Plasma concentrations of etomidate in 10 neonates at 2 and 6 h after delivery.

litre^{-1} less or 0.014 mmol litre^{-1} greater in the neonates exposed to etomidate compared with those given methohexitone.

Four of the five infants in the etomidate group with severe hypoglycaemia exhibited clinical symptoms such as irritability, while one did not. All three infants from the methohexitone group with extremely small blood glucose concentrations showed clinical signs of hypoglycaemia, as did two others who had normal blood glucose concentrations (table V). Although the neonates delivered by emergency Caesarean section had markedly smaller birth weights, they had neither smaller median blood glucose concentrations nor a greater incidence of hypoglycaemia.

Etomidate concentrations

Etomidate plasma concentrations were measured in 10 of the newborn infants (five each from the elective and the emergency section groups). Mean (SD) etomidate concentration in umbilical arterial blood was 83 (39) ng ml^{-1} (340 (160) nmol litre^{-1}) with a range of 42–154 ng ml^{-1} (172–631 nmol litre^{-1}), while the mean concentration in maternal plasma at the time of cord clamping was 198 (79) ng ml^{-1} (811 (324) nmol litre^{-1}) with a range of 77–352 ng ml^{-1} (316–1443 nmol litre^{-1}). Mean fetal-to-maternal etomidate concentration ratio (umbilical arterial: maternal venous (UA:MV)) was thus 0.48 (0.27). Mean etomidate concentration was 9.3 (4.2) ng ml^{-1} (38 (22) nmol litre^{-1}) 2 h after delivery and 6 (2.9) ng ml^{-1} (24.6 (15) nmol litre^{-1}) at 6 h postpartum. Figure 1 shows the temporal changes of the etomidate concentrations in each individual child.

DISCUSSION

We have shown that etomidate had a transient depressant effect on plasma cortisol concentrations in neonates, especially in infants subjected to intrauterine distress. Metabolic consequences of this impairment were not detected.

The choice of induction agent and its dose is of well-documented importance for the postpartum condition of the neonate delivered by Caesarean section [1, 2, 14, 15]. Thiopentone, methohexitone and etomidate are equally suitable for this purpose, and the last of these is an alternative for parturients for whom barbiturates are contraindicated [3]. However, etomidate inhibits cortisol synthesis in the adrenal cortex. The disturbing aspect of this fact is that circumstantial and experimental evidence shows a connection between inhibited corticosteroid synthesis and increased mortality in intensive care patients [16] and animals [17]. Although the neonate resembles neither the intensive care patient nor the animal model, it does represent a unique situation in mammalian life, insofar as the newborn infant has just undergone the transition from a state of continuous i.v. nutrition via the placenta to one characterized by intermittent enteral feeding. It must therefore be capable of adapting its metabolism to the maintenance of relatively constant blood sugar concentrations during periods of starvation by means of glycogenolysis and gluconeogenesis. In the immediate postpartum period this is accomplished by a surge of glucagon secretion which stimulates glycogenolysis [18]. Further starvation necessitates the actions of cortisol and catecholamines to stimulate gluconeogenesis. It is in this context that the extent and duration of corticosteroid synthesis inhibition in the newborn is important.

The plasma cortisol concentrations in the cord blood of our neonates after elective Caesarean section were very similar to those described previously [6, 7, 19]. The cortisol concentrations in the infants of our study delivered by emergency Caesarean section were slightly greater, and in a range comparable to values reported earlier [7, 20]. We also observed a slight increase 2 h postpartum in the infants whose mothers had been given methohexitone, in both the elective and the emergency groups. A similar increase has been described [6, 19], indicating that this is probably a typical occurrence after Caesarean section. Reddy, Pizer and Bull [6] attributed this increase to the decreasing influence of maternal oestrogen on fetal cortisol synthesis, but we believe that it is equally likely that it reflects the demands placed on intermediate metabolism for maintaining stable glucose concentrations.

The plasma cortisol concentrations were smaller in the infants whose mothers had been given etomidate compared with those receiving methohexitone. This significant difference may be attributed to the effect of etomidate which not only obtunded the increase observed in the methohexitone groups, but also caused concentrations to decrease. There was a reduction of more than 50% in the etomidate group at 2 h after delivery in neonates who had suffered intrauterine distress and had been delivered by emergency section. These results confirm the findings of Reddy, Pizer and Bull [6] that etomidate affects cortisol secretion in term neonates. Our results are an extension of their observations in that they show that the effect of etomidate on adrenal cortisol synthesis can no longer be detected in unstressed neonates 2 h after delivery. However, the effect of etomidate may be present at this time as, in stressed infants after emergency section, it was still demonstrable 2 h postpartum. Six hours is a reasonable estimate of the maximum duration of the inhibitory effects of etomidate in this setting. This agrees with the results of previous studies in adults [21].

The increased preoperative maternal cortisol concentrations may be interpreted as evidence of an increased activity of the pituitary–adrenal axis. This is in accordance with the increased ACTH, β-endorphin and cortisol concentrations described previously in parturients [20, 22]. The administration of etomidate was associated with a perioperative decrease in maternal plasma cortisol concentrations, while methohexitone had no such effect: At 2 h postpartum, the difference between the two groups was statistically significant, but it was no longer evident after 6 h. This is also in agreement with our data in adults [5].

The small blood concentrations of glucose observed 2 h after birth, irrespective of the induction agent, the indication for the Caesarean section or the birth weight, reflect the fact that Caesarean section neonates are subjected to only minor stress during delivery. As a result, moderate to severe hypoglycaemia was fairly frequent in all groups. There were insufficient data to allow the detection of any significant difference in the incidence. We consider that the most important clinical conclusion from these data would be to feed all Caesarean section neonates much earlier than is customary in our institution.

The minimum hypnotic plasma concentration of etomidate is approximately 250–300 ng ml^{-1} in adults [23]. Although there is no information on the hypnotic threshold concentrations in neonates, the etomidate concentrations in cord blood were considerably less than this in all infants. This is in agreement with the clinical assessment of the children, who were all quite awake and lively. The etomidate concentration data at birth are in good agreement with those reported by Gregory and Davidson (24), who found mean (SD) maternal concentrations of 198.8 (73.9) ng ml^{-1} and umbilical arterial concentrations of 62.9 (33.3) ng ml^{-1} using a slightly less sensitive etomidate assay with similar precision. The smaller neonatal concentrations in their study may be attributable to the fact that incision-to-delivery times were two to four times longer than in the present study. The etomidate concentrations at delivery were definitely greater than the 110 nmol litre^{-1} (27 ng ml^{-1}) at which there is a 50% inhibition of cortisol synthesis in adults [21]. At 2 h postpartum, the umbilical arterial etomidate concentrations had decreased to less than this in all of the infants, and at 6 h only three neonates had an etomidate plasma concentration greater than the minimum effective value of 20 nmol litre^{-1}. The neonatal plasma etomidate concentrations are not amenable to formal kinetic analysis; however, the mean concentration decreased by about 40% from the 2nd to the 6th hour. This approximate half-life of 6 h is comparable to that reported by de Ruiter and colleagues [25] in surgical patients, although longer than the half-life observed by Schüttler and colleagues [26] in adult volunteers.

We have shown that the clinical condition of neonates delivered by Caesarean section was comparable after induction of general anaesthesia with either etomidate or methohexitone. Etomidate did cause a suppression of plasma cortisol concentrations in neonates, but the effect is only transient. The inhibited cortisol synthesis was not associated with a marked disturbance of glucose homeostasis; but the data were insufficient to decide if it caused a significantly increased incidence of hypoglycaemia. We conclude that there is no evidence that would preclude the use of etomidate for induction of anaesthesia for Caesarean section. However, we would recommend early feeding for all infants delivered by Caesarean section, regardless of the anaesthetic given in order to avoid hypoglycaemia.

REFERENCES

1. Datta S, Alper MH. Anesthesia for Cesarean section. *Anesthesiology* 1980; **53**: 142–160.
2. Morgan M, Holdcroft A, Whitwam JG. Comparison of thiopentone and methohexitone as induction agents for Caesarean section. *Anaesthesia and Intensive Care* 1980; **8**: 431–435.
3. Downing JW, Buley RJ, Brooke-Utne JG, Houlton PC. Etomidate for induction of anaesthesia at Caesarean section: comparison with thiopentone. *British Journal of Anaesthesia* 1979; **51**: 135–140.
4. Duthie DJR, Fraser R, Nimmo WS. Effect of induction of anaesthesia with etomidate on corticosteroid synthesis in man. *British Journal of Anaesthesia* 1985; **57**: 156–159.
5. Crozier TA, Beck D, Schlaeger M, Wuttke W, Kettler D. Endocrinological changes following etomidate, midazolam, or methohexital for minor surgery. *Anesthesiology* 1987; **66**: 628–635.
6. Reddy BK, Pizer B, Bull PT. Neonatal serum cortisol suppression by etomidate compared with thiopentone, for elective Caesarean section. *European Journal of Anaesthesiology* 1988; **5**: 171–176.
7. Kohno H, Furuhashi N, Fukaya T, Tachibana Y, Shinkawa O, Suzuki M. Serum cortisol levels of maternal vein, umbilical artery, and umbilical vein classified by mode of delivery. *Gynecologic and Obstetric Investigation* 1984; **17**: 301–308.
8. Falconer AD, Poyser LM. Fetal sympatho–adrenal mediated metabolic responses to parturition. *British Journal of Obstetrics and Gynaecology* 1986; **93**: 747–753.
9. Artavia-Loria E, Chaussain JL, Bougnères PF, Job JC. Frequency of hypoglycaemia in children with adrenal insufficiency. *Acta Endocrinologica* 1986; **113** (Suppl. 279): 275–278.
10. Shnider SM, Levinson G. Obstetric anesthesia. In: Miller RD, ed. *Anesthesia*, 2nd Edn. New York, London, Edinburgh, Melbourne: Churchill Livingstone, 1986; 1710.
11. Khawaja AA. A rapid intubation technique for prevention of aspiration during induction of anaesthesia. *British Journal of Anaesthesia* 1971; **43**: 980–983.
12. De Boer AG, Smeekens JB, Breimer DD. Assay of etomidate in plasma by capillary gas chromatography with nitrogen-selective detection. *Journal of Chromatography* 1979; **162**: 591–597.
13. Moses LE. Confidence limits from rank tests. *Technometria* 1965; 7: 257–260 (cited in: Leinert GA. *Verteilungsfreie Methoden in der Biostatistik*, Vol. 2. Meisenheim, Germany: Verlay Anton Hain, 1978; 97–100.
14. Bland BA, Lawes EG, Duncan PW, Warnell I, Downing JW. Comparison of midazolam and thiopental for rapid sequence anesthetic induction for elective Cesarean section. *Anesthesia and Analgesia* 1987; **66**: 1165–1168.
15. Holdcroft A, Robinson MJ, Gordon H, Whitwam JG. Comparison of the effect of two induction doses of methohexitone on infants delivered by elective Caesarean section. *British Medical Journal* 1974; **2**: 472–475.
16. Ledingham IMcA, Watt I. Influence of sedation on mortality in critically ill multiple trauma patients. *Lancet* 1983; **1**: 1270.

17. Barton RN, Little RA. Effects of inhibition of adrenal steroidogenesis on compensation of fluid loss and on survival after limb ischaemia in the rat. *Journal of Endocrinology* 1978; **76**: 293–302.
18. Sperling MA. Integration of fuel homeostasis by insulin and glucagon in the newborn. *Monographs in Paediatrics* 1982; **16**: 39–58.
19. Pohjovouri M, Rovamo L, Laatikainen T. Plasma immunoreactive beta-endorphin and cortisol in the newborn infant after elective Caesarean section and after spontaneous labour. *European Journal of Obstetrics, Gynecology and Reproductive Biology* 1985; **19**: 67–74.
20. Bacigalupo G, Langner K, Schmidt S, Saling E. Plasma immunoreactive beta-endorphin, ACTH, and cortisol concentrations in mothers and their neonates immediately after delivery—their relationship to the duration of labor. *Journal of Perinatal Medicine* 1987; **15**: 45–52.
21. Crozier TA, Beck D, Wuttke W, Kettler D. *In vivo* suppression of steroid synthesis by etomidate is concentration-dependent. *Anaesthesist* 1988; **37**: 337–339.
22. Abboud TK, Sarkis F, Hung TT, Khoo SS, Varakian L, Henriksen E, Noueihed R, Goebelsmann U. Effects of epidural anesthesia during labor on maternal plasma beta-endorphin levels. *Anesthesiology* 1983; **59**: 1–5.
23. Schüttler J, Stoeckel H, Wilms M, Schwilden H, Lauven PM. Infusion model for etomidate. *Anaesthesist* 1980; **29**: 662–666.
24. Gregory MA, Davidson DG. Plasma etomidate levels in mother and fetus. *Anaesthesia* 1991; **46**: 716–718.
25. de Ruiter G, Popescu DT, de Boer AG, Smeekens JB, Breimer DD. Pharmacokinetics of etomidate in surgical patients. *Archives Internationales de Pharmacodynamie et de Thérapie* 1981; **249**: 180–188.
26. Schüttler J, Wilms M, Lauven PM, Stoeckel H, König A. Pharmacokinetics of etomidate in man. *Anaesthesist* 1980; **29**: 658–661.

British Journal of Anaesthesia 1993; 70: 54–57

NITROUS OXIDE-MEDIATED ACTIVATION OF THE EEG DURING ISOFLURANE ANAESTHESIA IN PATIENTS

A. YLI-HANKALA, L. LINDGREN, T. PORKKALA AND V. JÄNTTI

SUMMARY

We have studied the effects of nitrous oxide on EEG burst suppression patterns during stable isoflurane anaesthesia in 13 ASA I patients. After induction of anaesthesia with propofol, the concentration of isoflurane was increased with continuous EEG monitoring to burst suppression level (mean end-tidal concentration of isoflurane, 1.7 (SD 0.2) %), and kept constant during the study. During surgery, isoflurane in air and oxygen ($F_{I_{O_2}}$ 0.35), or isoflurane in 65% nitrous oxide in oxygen were given to each patient for 30 min, in random order. EEG was recorded and digitized off-line. The proportion of EEG suppression time was measured after a washin or washout period of at least 15 min for nitrous oxide. There was a significant decrease in the proportion of EEG suppression time (from 69.5 to 43.7%) when air was replaced by nitrous oxide. We conclude that the EEG effects of isoflurane and nitrous oxide are not additive and that nitrous oxide opposes the depression of isoflurane on the central nervous system. (Br. J. Anaesth. 1993; **70**: 54–57)

KEY WORDS

Anaesthetic techniques: inhalation. Anaesthetics, gases: nitrous oxide. Anaesthetics, volatile: isoflurane. Brain: electroencephalography.

The effects of nitrous oxide on the electroencephalogram (EEG) during inhalation anaesthesia have been studied extensively. In a study using spectral analysis [1], there were no changes in the EEG from nitrous oxide when it was used in combination with other anaesthetics. Other studies, however, have reported a reduction of total EEG spectral power [2], or an increase in fast frequency EEG power bands [3] when inhalation anaesthesia was supplemented with nitrous oxide.

At 1.5–2.0 minimal alveolar concentration (MAC) of isoflurane anaesthesia, the EEG shows a burst suppression pattern—relatively silent EEG periods interrupted by high amplitude bursts [4]—which appear synchronously in the whole cortex [5]. When anaesthesia is deepened further, duration of suppressions increases and, finally, an isoelectric EEG results [4]. We have demonstrated that nitrous oxide slows the rhythm of EEG activity during isoflurane anaesthesia in man, without appearance of an EEG burst suppression pattern, when 1.5% end-tidal isoflurane anaesthesia is deepened with 65% nitrous oxide [6]. Recent animal studies have demonstrated the activation of EEG by nitrous oxide during burst suppression isoflurane anaesthesia [7, 8]. Rampil and colleagues have reported that nitrous oxide activates EEG during desflurane burst suppression anaesthesia in volunteers [9]. The effect of nitrous oxide on isoflurane burst suppression has not, however, been studied in humans. Therefore, we studied the effect of nitrous oxide on the EEG burst suppression pattern during isoflurane anaesthesia and surgery in healthy patients.

PATIENTS AND METHODS

The study was approved by the Ethics Committee of Helsinki University Central Hospital. Thirteen healthy ASA I patients (table I) gave informed consent.

Anaesthesia

Patients were premedicated with oral diazepam 0.2 mg kg^{-1} 90 min before induction of anaesthesia with propofol (mean) 1.8 (SD 0.2) mg kg^{-1} i.v. Vecuronium was given for neuromuscular block and no anticholinergic agent was used. Positive pressure ventilation was performed via a tracheal tube, using a Servo respirator (Siemens–Elema, Sweden). Tidal volume was adjusted to maintain normocapnia (end-tidal carbon dioxide 5.0 kPa), measured with a Datex Capnomac monitor (Instrumentarium Ltd, Fin-

TABLE I. *Patient characteristics and operations (mean (SD) or range). Data for 13 patients*

Sex (M/F)	9/4
Age (yr)	36.8 (26–49)
Weight (kg)	72 (19)
Height (cm)	164 (15)
Operation	
Breast surgery	4
Abdominal surgery	9

ARVI YLI-HANKALA*, M.D.; LEENA LINDGREN, M.D.; Department of Anaesthesia, Fourth Department of Surgery, Helsinki University Central Hospital, Kasarmikatu 11, SF-00130 Helsinki, Finland. TIMO PORKKALA, M.D. (Department of Anaesthesia); VILLE JÄNTTI, M.D. (Department of Clinical Neurophysiology); Tampere University Hospital, P.O. Box 2000, SF-33521 Tampere, Finland. Accepted for Publication: August 25, 1992.

* Present address, for correspondence: Department of Clinical Sciences, Tampere University, P.O. Box 607, SF-33101 Tampere, Finland.

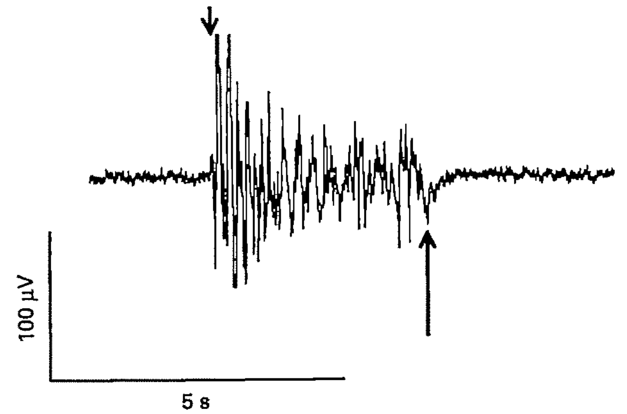


FIG. 1. Definition of the beginning of EEG burst and suppression. Burst onset at the short, down-pointing arrow. Suppression onset at the long, up-pointing arrow. Note the EEG notch at the beginning of suppression.

land). Arterial pressures were measured non-invasively with a Datex Normocap monitor at intervals of 3 min. Temperature was measured from the nasopharynx and normothermia was maintained using warming blankets. All patients were horizontal and supine during the study.

At first, isoflurane was delivered with oxygen in air ($F\mathrm{I}_{\mathrm{O}_2}$ 0.35). Isoflurane concentrations were monitored on-line (Datex Capnomac). For each patient, the analyser was calibrated with a known concentration of isoflurane and carbon dioxide, and at 0%.

All the recordings were performed during the surgical procedure. After induction of anaesthesia, we waited 45 min to allow the effect of propofol to disappear. EEG was monitored continuously. Anaesthesia was deepened gradually to a point at which burst suppression occurred on the EEG (1.7 (0.2)% end-tidal isoflurane), and then kept constant during the study.

During two 30-min periods, isoflurane in air and oxygen ($F\mathrm{I}_{\mathrm{O}_2}$ 0.35), and isoflurane and 65% nitrous oxide in oxygen ($F\mathrm{I}_{\mathrm{O}_2}$ 0.35) was delivered to each patient. The initial gas mixture was selected at random. In seven patients, air and oxygen were given before challenge with nitrous oxide and oxygen, while the other patients received nitrous oxide and oxygen first. Analyses were performed on EEG data recorded after a washin or washout period of 15 min for nitrous oxide.

Signal recording and analysis

Silver–silver chloride dome EEG electrodes were placed in C_z and F_z positions (International 10–20 System). EEG was amplified and monitored with Datex ABM monitor (Instrumentarium, Finland, bandwidth 1.5–25 Hz (−3 dB)) and recorded on tape (Racal FM tape recorder, Racal, England). Event marks, such as turning on/off nitrous oxide, also were recorded on tape.

EEG and event mark signals were digitized off-line at 200 samples s^{-1} per channel to a PC-compatible microcomputer. EEG burst–onset points and suppression-onset points were selected manually with a cursor on the computer screen. This selection was always performed by one of the authors (T.P.) unaware of the order of randomization. End-point of the burst was defined as the EEG notch, which is seen at the beginning of suppression (fig. 1).

As the recordings were made during routine surgical procedures, artefacts occurred randomly in the signal. Only bursts and suppressions completely devoid of artefact were included in the analysis. Recordings were analysed for duration of suppression, which was expressed as percentage of the sum of artefact-free bursts and suppressions in a 15-min period.

Statistics

Data were analysed using the computer software program BMDP (University of California, Berkeley, U.S.A.). The comparisons were tested with Wilcoxon's matched-pairs signed-ranks test. The data are given as mean (SD). $P < 0.05$ was considered statistically significant.

RESULTS

The duration of EEG bursts and suppressions occurring in one patient is presented in figure 2. In the study group, the proportion of EEG suppression

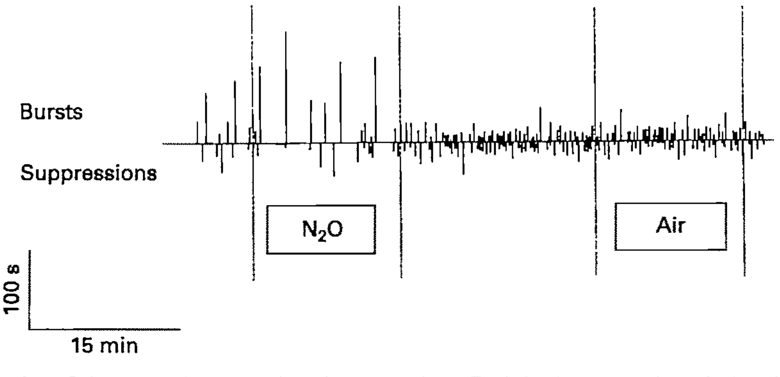


FIG. 2. Duration of EEG bursts and suppressions in one patient. Both horizontal and vertical scales present time. Horizontal line = baseline. Bursts are presented as lines upwards, suppressions as down-pointing lines from the baseline. The long dotted vertical lines delimit the two EEG analysis periods. N_2O = EEG analysis period during isoflurane–nitrous oxide–oxygen anaesthesia. Air = EEG analysis period during isoflurane–air–oxygen anaesthesia. The proportion of EEG suppression time was evaluated during nitrous oxide inhalation and after a wash-out period of 20 min for nitrous oxide. Note the rapid reduction in the duration of EEG bursts, when nitrous oxide exposure was replaced by air at the end of the first analysis period.

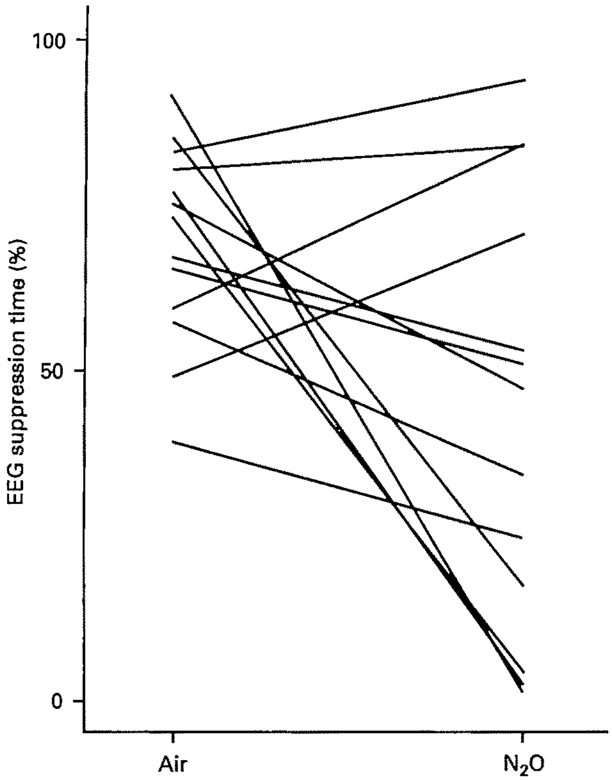


FIG. 3. Proportion of EEG suppression time in 13 patients during isoflurane in air (Air) and during isoflurane in nitrous oxide (N_2O) analysis period. Each line represents one individual. The initial gas mixture (air or nitrous oxide) was selected at random.

time was 69.5 (15.1) % during isoflurane–air–oxygen anaesthesia. This proportion decreased to 43.7 (33.1) % during isoflurane–nitrous oxide–oxygen anaesthesia ($P < 0.05$) (fig. 3). Mean length of EEG bursts changed from 10 (7) s to 24.8 (28) s ($P < 0.01$), and that of EEG suppressions from 22.7 (13) s to 20.8 (23) s (ns), when air was replaced by nitrous oxide.

The course of surgery was uneventful and without major bleeding in all patients. Mean arterial pressure and heart rate at the end of isoflurane–air–oxygen recording period were 73 (18) mm Hg and 82 (13) beat min^{-1}, respectively. The same figures at the end of nitrous oxide inhalation were 70 (16) mm Hg and 76 (13) beat min^{-1}, respectively (ns).

DISCUSSION

The present study shows that, when burst suppression isoflurane anaesthesia was supplemented by 65 % nitrous oxide, the duration of EEG suppression decreased and the duration of bursts increased—that is, nitrous oxide activated the EEG during burst suppression.

The activation of isoflurane EEG by nitrous oxide, with [7] or without [8] changes in cerebral blood flow (CBF), has been demonstrated in animals. In their recent study in patients, Algotsson and colleagues [10] reported an increase in CBF, with a decrease in cerebral vascular resistance and an activation pattern in the EEG when 1.7 % isoflurane–air was replaced by 0.85 % isoflurane–nitrous oxide–oxygen. However, the EEG was not studied during constant concentrations of isoflurane. The present result, with constant isoflurane concentrations, is in accordance with our earlier study [6] showing that, although the frequency of EEG rhythm decreased when 65 % nitrous oxide was added to 1.5 % isoflurane anaesthesia, EEG suppressions were not seen. In the present study, addition of 0.7 % (0.6 MAC) isoflurane instead of nitrous oxide, would probably have produced continuous EEG suppression in most of our patients [4].

The mechanism of activation of the EEG by nitrous oxide is interesting. Algotsson and colleagues [10] proposed a secondary effect of nitrous oxide on the brainstem reticular centres, which could also explain the result obtained in our study.

Four of our 13 patients showed an increase in the duration of EEG suppression during nitrous oxide. In two of these subjects the operation was abdominal, while in the two others it was breast surgery. The level of surgical stimulation in intra-abdominal surgery may differ from that of breast surgery. The type of surgery, however, seemed not to have any influence on the results.

Previous human studies on the effect of nitrous oxide on the EEG have often applied spectral analysis [1–3, 6]. Some of these results may also be interpreted as nitrous oxide-induced activation of the EEG. Spectral analysis is, however, sensitive to the bandpass characteristics of the recording system [11]. Furthermore, in addition to the spectral content of EEG, changes may occur in the topographical distribution and waveform of the EEG. This was demonstrated in our earlier study [6] which gave controversial results: nitrous oxide slowed the rhythm of EEG activity during isoflurane anaesthesia. Visual inspection of the raw EEG signal, however, showed that this was caused by frontal rhythmic delta activity, which may be interpreted as lightening of anaesthesia [12]. The waveform of the raw EEG signal, and transients (spikes, short suppressions), are lost in transformation to the power spectrum. Moreover, power spectrum analysis assumes a stationary signal, which is not present during burst suppression. Time domain analysis of EEG is thus more suitable for burst suppression EEG studies.

We used propofol for induction of anaesthesia. Propofol is claimed to have an effect on the EEG for only about 10 min after induction [13]. In our study, 45 min elapsed from administration of propofol to the recordings. Thus it is unlikely that propofol had any effect on the EEG during our measurements.

The burst involves d.c. shift in the EEG, which could be seen with increased bandwidth—a longer time constant in recording [14]. Usually, because of the high-pass filter, this d.c. shift is seen only as a small notch in the end of the burst. We used that notch as the definition of the suppression onset point, as it marks the end of the burst, which otherwise is difficult to determine.

In conclusion, we have shown that, during isoflurane burst suppression, nitrous oxide activated the EEG. The effect of nitrous oxide should be taken into consideration when isoflurane burst suppression is used as an indicator for depth of anaesthesia.

ACKNOWLEDGEMENTS

This study was supported by a grant from the Academy of Finland.

REFERENCES

1. Pichlmayr I, Lips U, Künkel H. *The Electroencephalogram in Anesthesia. Fundamentals, Practical Applications, Examples.* New York: Springer-Verlag, 1984.
2. Brandt L, Dick W, Erdmann K. Nitrous oxide influences EEG changes induced by halothane, enflurane and isoflurane. *Anesthesiology* 1985; **63** (3A): A409.
3. Smith NT, Hoff BH, Rampil IJ, Sasse FJ, Flemming DC. Does thiopental or N_2O disrupt the EEG during enflurane? *Anesthesiology* 1979; **51**: S5.
4. Eger EI II, Stevens WC, Cromwell TH. The electroencephalogram in man anesthetized with Forane. *Anesthesiology* 1971; **35**: 504–508.
5. Julien RM, Kavan EM. Electrographic studies of isoflurane (Forane®). *Neuropharmacology* 1974; **13**: 677–681.
6. Yli-Hankala A. The effect of nitrous oxide on EEG spectral power during halothane and isoflurane anaesthesia. *Acta Anaesthesiologica Scandinavica* 1990; **34**: 579–584.
7. Kaieda R, Todd MM, Warner DS. The effects of anesthetics and Pa_{CO_2} on the cerebrovascular, metabolic, and electroencephalographic responses to nitrous oxide in the rabbit. *Anesthesia and Analgesia* 1989; **68**: 135–143.
8. Roald OK, Forsman M, Heier MS, Steen PA. Cerebral effects of nitrous oxide when added to low and high concentrations of isoflurane in the dog. *Anesthesia and Analgesia* 1991; **72**: 75–79.
9. Rampil IJ, Lockhart SH, Eger EI, Yasuda N, Weiskopf RB, Cahalan MK. The electroencephalographic effects of desflurane in humans. *Anesthesiology* 1991; **74**: 434–439.
10. Algotsson L, Messeter K, Rosén I, Holmin T. Effects of nitrous oxide on cerebral haemodynamics and metabolism during isoflurane anaesthesia in man. *Acta Anaesthesiologica Scandinavica* 1992; **36**: 46–52.
11. Prior PF, Maynard DE. *Monitoring Cerebral Function.* Amsterdam: Elsevier, 1986.
12. Daube JR, Harper CM, Litchy WJ, Sharbrough FW. Intraoperative monitoring. In: Daly DD, Pedley TA, eds. *Current Practice of Clinical Electroencephalography*, 2nd Edn. New York: Raven Press, 1990; 739–779.
13. Shütter J, Stoeckel H, Schwilden H. Pharmacokinetic and pharmacodynamic modelling of propofol ("Diprivan") in volunteers and surgical patients. *Postgraduate Medical Journal* 1985; **61** (Suppl. 3): 53–54.
14. Jäntti V, Yli-Hankala A, Baer G, Porkkala T. Slow potentials of EEG burst suppression pattern during anaesthesia. *Acta Anaesthesiologica Scandinavica* 1992; (in press).

British Journal of Anaesthesia 1993; 70: 58–62

COMPARISON OF THORACIC ELECTRICAL BIOIMPEDANCE AND THERMODILUTION FOR THE MEASUREMENT OF CARDIAC INDEX IN PATIENTS WITH SEVERE SEPSIS

J. D. YOUNG AND P. McQUILLAN

SUMMARY

Cardiac index was measured using thoracic bioimpedance (CIbi) and thermodilution (CItd) in 19 patients with proven sepsis, undergoing artificial ventilation of the lungs. There was a poor correlation between the techniques ($r = 0.36$, 242 data sets, regression line CIbi = 0.16 CItd + 2.56 litre min^{-1} m^{-2}). The overall bias (CItd–CIbi) was 1.69 litre min^{-1} m^{-2} with limits of agreement (precision) of +4.17 to −0.79 litre min^{-1} m^{-2}. In individual patients the bias was from −0.46 to 4.56 litre min^{-1} m^{-2} with the limits of agreement from ±0.29 to ±2.55 litre min^{-1} m^{-2} around the bias values. The two techniques cannot be used interchangeably in this group of patients. (Br. J. Anaesth. 1993; **70**: 58–62)

KEY WORDS

Complications: sepsis. Measurement techniques: thermodilution, thoracic bioimpedance. Monitoring: cardiac index.

Variations in the electrical impedance of the thorax to an alternating current (Z) which occur synchronously with the cardiac cycle were observed nearly 40 years ago [1]. The first use of this phenomenon to measure stroke volume and cardiac output was described by Nyboer [2] and developed by Kubicek and colleagues [3, 4]. The method uses the maximum rate of change of thoracic bioimpedance, ($\delta Z/\delta t$max) during systole to calculate stroke volume. The original equation used by Kubicek and colleagues was modified by Bernstein [5] to remove assumptions about body morphology. This equation is used to calculate stroke volume in a commercially available impedance cardiograph, the NCCOM-3 (BoMed Medical Manufacturing Ltd), which also measures heart rate and then calculates cardiac output and index. It is non-invasive, requiring only the application of 10 electrodes to the neck and chest, and provides a continuous estimate of cardiac index. The device has many potential applications, for example a continuous measure of cardiac output combined with a pulse oximeter and a mixed venous oximetry pulmonary artery catheter would allow continuous monitoring of oxygen delivery and consumption. However, during initial assessment of this device in our Intensive Care Unit, it became apparent that in patients with severe sepsis the cardiac indexes determined by thermodilution and by bioimpedance often differed. We report a comparative study of the NCCOM-3 and thermodilution for measurement of cardiac index in patients with severe sepsis.

PATIENTS AND METHODS

The study was approved by the institutional Ethics Committee. Patients were selected for study if they already had a pulmonary artery catheter placed for haemodynamic assessment and clinical signs consistent with systemic sepsis [6], with either microbiological evidence of a source of sepsis or positive blood cultures. All patients were undergoing mechanical ventilation of the lungs using intermittent mandatory ventilation or controlled ventilation. No alterations in therapy were made for the purpose of the study.

We studied 19 patients, usually twice daily whilst they were clinically septic. Five patients had a perforated viscus, two had pancreatitis, four had pulmonary infection, four had sepsis following trauma, two had infection following aortic aneurysm surgery, one patient had toxic shock syndrome and one had an infected hip arthroplasty. A total of 242 pairs of measurements were made.

Cardiac index was determined from thoracic bioimpedance changes using the NCCOM-3 device (revision 6 software [7]). Eight current injection and voltage sensing electrodes were placed on the neck and thorax and two additional electrodes were placed on the right sternal border and over the apex beat to provide a high-quality ECG signal. All the electrodes were placed according to the manufacturer's instructions, and electrodes were left in place between measurements unless they interfered with the patient's care. Neck dressings for internal jugular catheters were removed to allow electrode positioning where required. The ECG and bioimpedance ($\delta Z/\delta t$) signals were taken from the analog output port on the NCCOM-3 to a twin-channel chart recorder (Lectromed Ltd) to allow a visual check on the signal quality. The NCCOM-3 digital output

---

J. D. YOUNG*, F.R.C.ANAES.; P. McQUILLAN, F.R.C.ANAES.; Intensive Care Unit, Nuffield Department of Anaesthetics, John Radcliffe Hospital, Headley Way, Oxford. Accepted for Publication: July 17, 1992.

*Present address, for correspondence: Nuffield Department of Anaesthetics, Radcliffe Infirmary, Woodstock Road, Oxford OX2 6HE.

port was connected to a "Thinkjet" printer (Hewlett–Packard Ltd) to provide a permanent printed record. The patient's sex, height and weight were introduced into the NCCOM-3 keyboard, and the calculated body surface area recorded. Cardiac index was taken as the average during 60 heartbeats accepted by the NCCOM-3 recorded at the same time as the thermodilution measurements.

Thermodilution determinations of cardiac output were performed using a COM-1 cardiac output computer (Edwards Laboratories) with a closed injectate delivery system and in-line temperature sensor ("CO-set" system, Edwards Laboratories). Injectate temperatures were always less than 10 °C, and injections were made manually during expiration. Measurements were always made by one of the authors; the average of three measurements was used. Cardiac output was converted to cardiac index using the body surface area calculated by the NCCOM-3 thoracic bioimpedance computer.

The results were analysed using linear regression analysis and by the method described by Bland and Altman [8] for comparing two methods of measurement, which allows bias and precision to be assessed numerically and graphically.

The NCCOM-3 calculates cardiac output by using the formula:

$$\dot{Q} = \mathrm{HR} \times V_{\mathrm{EPT}} \times \mathrm{VET} \times \delta Z/\delta t\mathrm{max}/Z^0$$

where $\dot{Q}$ = cardiac output (litre min^{-1}); HR = heart rate (beat min^{-1}); VET = ventricular ejection time (s); Z^0 = baseline thoracic impedance (Ω); $\delta Z/\delta t\mathrm{max}$ = maximum rate of change of thoracic impedance during systole (Ω s^{-1}). V_{EPT} is the volume of electrically participating tissue, calculated as:

$$V_{\mathrm{EPT}} = d \times (0.17 \times H)^3/4.25$$

where H = height (cm); d = ratio of actual to ideal weight multiplied by the ratio of the calculated thoracic blood volume to the calculated ideal thoracic blood volume [5].

The cardiac output is scaled with the body surface area calculated from height and weight (body surface area = [height in cm]$^{0.725}$ × [weight in kg]$^{0.425}$ × 0.00718) to obtain cardiac index. To determine if one factor caused the difference or ratio between cardiac index measured by the two techniques, both the difference and ratio of the two stroke volume measurements were regressed against the values for heart rate, height, weight, Z^0 and ventricular ejection time (determined by the NCCOM-3) using multiple linear regression. The ventricular ejection time was also computed from the heart rate using the formula described by Weissler and Garrard [9] and compared with the ratio and difference of the two stroke volume measurements using linear regression. The stroke volume was used for the regressions to minimize mathematical linkage of the values being regressed.

RESULTS

The scatter plot of cardiac index measured by bioimpedance against cardiac index measured by thermodilution is shown in figure 1. The regression line is $y = 0.16x + 2.56$; the correlation coefficient 0.36. There is a large scatter in the results.

If the data are presented as the difference between simultaneous cardiac index estimates plotted against the mean of the values, a plot as shown in figure 2 results [8]. This accentuates what the regression line revealed: there is generally an increasing error with increasing cardiac index. The bias is 1.69 litre min^{-1} m^{-2} with limits of agreement of ±2.48 (+4.17 to −0.79) litre min^{-1} m^{-2}. The limits of agreement represent the 95% confidence limits for the estimate of a value of cardiac index that would be recorded by bioimpedance for a given value of cardiac index determined by thermodilution in the range 2–8 litre min^{-1} m^{-2}.

The linear regression line for cardiac index measured by the NCCOM-3 on cardiac index measured by thermodilution has a large offset (2.56 litre min^{-1} m^{-2}) and a low gradient (an increase of 0.16 litre min^{-1} m^{-2} in the NCCOM-3 reading for every litre min^{-1} m^{-2} increase in the thermodilution value). If this is regarded as a "calibration" error in the NCCOM-3, this can be corrected mathe-

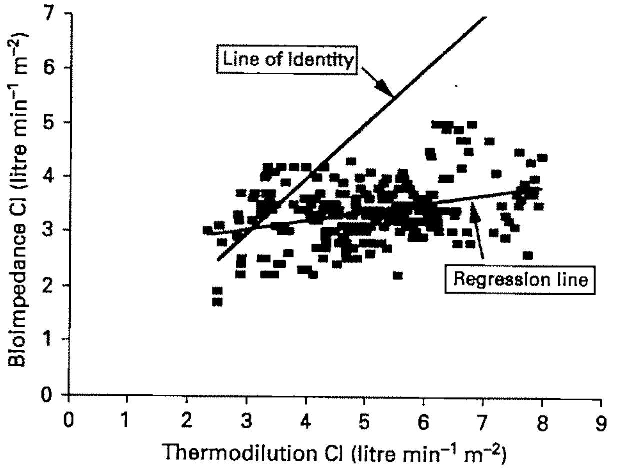


FIG. 1. Cardiac index measured by bioimpedance plotted against cardiac index measured simultaneously by thermodilution.

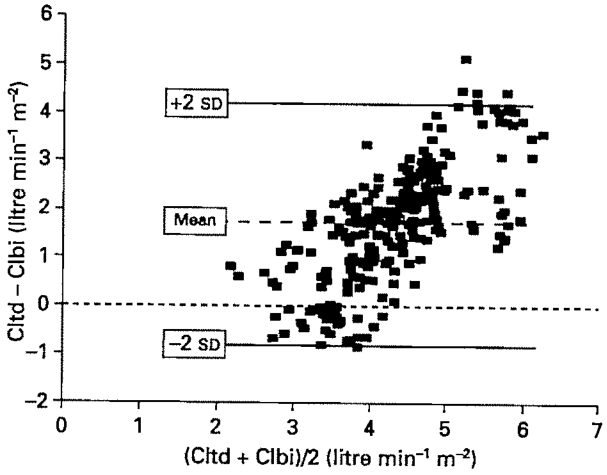


FIG. 2. Difference between simultaneous measurements of cardiac index measured by thermodilution (CItd) and by bioimpedance (Cbi) plotted against the mean of the two values. The mean difference (the bias) and the limits of agreement (±2 SD of the difference values) are also shown.

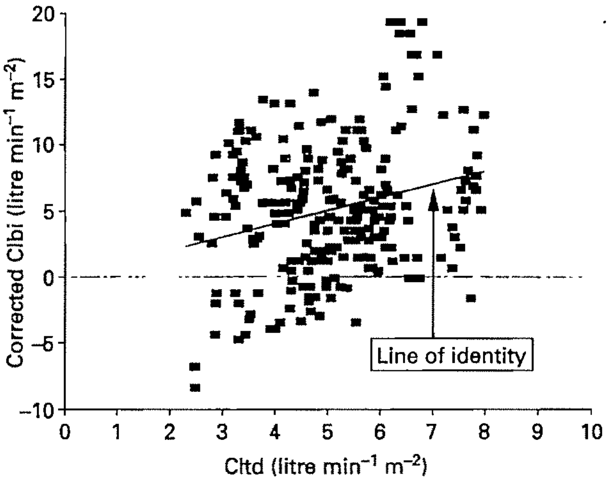


FIG. 3. Cardiac index measured by thermodilution (CItd) plotted against the "corrected" cardiac index measured simultaneously by bioimpedance (CIbi). The bioimpedance cardiac index was corrected using the regression of the thermodilution values on the bioimpedance values, so the line of identity and the regression line coincide.

matically—the regression of thermodilution on NCCOM-3 cardiac index values. The resulting plot is shown in figure 3. Although the regression line now has a gradient of 1 and an offset of 0, the correction has not improved the scatter of the results around the regression line. Thus, although the bias has now been eliminated, there is virtually no change in the limits of agreement determined by the Bland and Altman technique (±2.46 litre min^{-1} m^{-2}).

The mean value for baseline thoracic impedance (Z^0) was 12.4 (SD 3.2) Ω (range 6.2–20.2 Ω). Neither the difference between the values for stroke volume measured by thermodilution and bioimpedance, nor the ratio of the two values showed any dependence on heart rate, Z^0 or ventricular ejection time, either measured by the NCCOM-3 or calculated from the heart rate. Both the difference and ratio of the two values for stroke volume were dependent on height and weight ($P < 0.0001$). However, the value for stroke volume measured by thermodilution also correlated strongly with height and weight (both $P < 0.0001$), so this probably represents an increasing difference and ratio of the two values for stroke volume with increasing stroke volume, and not an error dependent on height or weight.

DISCUSSION

There have been many human studies comparing measurement of stroke volume or cardiac output using bioimpedance with other established methods in volunteers or patients. Bioimpedance measurements of stroke volume correlate with measurements made by left ventriculograms [10], by echocardiography [11, 12], by the direct or indirect Fick method [13–18] and by dye dilution [4, 14, 19–22], although there is a large range of correlation coefficients (0.29–0.99) and the regression lines are often displaced from the line of identity.

The widespread use of pulmonary artery catheters in critical care units has facilitated comparison of cardiac output measured by thermodilution and bioimpedance in seriously ill patients [23–30]. These comparisons showed regression lines with gradients less than 1 (0.28–0.98) and positive intercepts (0.35–2.61 litre min^{-1}). Thus the bioimpedance technique would be expected to indicate a cardiac output that exceeds the output measured by thermodilution at low cardiac outputs, but would underestimate at higher cardiac outputs. The correlation coefficients for these studies ranged from 0.41–0.91. All these studies with the exception of that by Donovan and colleagues [29] used the NCCOM-3 impedance cardiograph.

The use of correlation coefficients to compare two methods of measurement has been criticized as they do not give any indication of the error that can be expected when one method of measurement is substituted for another. To overcome this, the method of Bland and Altman [8] may be used to estimate the bias and precision of one method compared with another. Gotshall, Wood and Miles [24] and Wong and colleagues [26] used the technique to compare cardiac output measured by thermodilution and bioimpedance in critically ill patients. They showed bias values of −0.67 and −0.03 litre min^{-1} and "limits of agreement" of +2.77 to −4.11 litre min^{-1} and +3.24 to −3.30 litre min^{-1}, respectively. As a result, both groups urged caution in the use of bioimpedance as a monitor of absolute values of cardiac output.

The comparison of thermodilution and bioimpedance measurements of cardiac output in patients with sepsis has not been examined directly. Bernstein [27] observed that in vasodilated septic patients the bioimpedance method underestimated cardiac output, and suggested this was caused by shunting of the current via vasodilated skin and muscle, thus bypassing the lungs and great vessels. Wong and colleagues [26] analysed a subgroup of septic patients and found a correlation coefficient of 0.73 and a regression line close to the line of identity, and concluded that sepsis was not a factor likely to influence the correlation between thermodilution and bioimpedance measurements of cardiac output.

In this study we found a very poor correlation between the cardiac index measured by bioimpedance and thermodilution. The bioimpedance method overestimated at low cardiac index and markedly underestimated at high cardiac index, with a large scatter in the results. The correlation coefficient is the smallest reported for any comparison of bioimpedance and thermodilution methods on any group of critically ill patients. The limits of agreement using Bland and Altman's technique are very wide, implying the techniques are not interchangeable. Even if the bioimpedance results are mathematically corrected to cause the regression line to match the line of identity, the scatter of the results is such that it is impossible to replace thermodilution methods with bioimpedance.

We used accepted methods for measurement of cardiac index by thermodilution and tried to ensure that cardiac index determinations using bioimpedance and thermodilution were made over as many of the same cardiac cycles as possible. No patient had tricuspid incompetence as judged by the central venous pressure trace. Cold injectate was used, to minimize errors. The thermodilution technique was identical to that used in other comparative studies of thermodilution and bioimpedance that have shown far better correlation. In a study performed just before this study in the same Intensive Care Unit using the same equipment and techniques on non-septic, artificially ventilated patients, Jewkes and colleagues [31] showed a correlation coefficient of 0.72 and limits of agreement of -2.6 to $+0.89$ litre min^{-1} for cardiac output. Thus we attribute the large discrepancy in the two methods in this study partially to errors in the bioimpedance technique specific to septic patients. However, the accuracy of thermodilution measurements of cardiac output in patients with sepsis has not been investigated by comparison with other techniques except suprasternal Doppler flow measurement [26], so there is a small chance that errors in thermodilution measurements caused the discrepancy.

The mean thoracic bioimpedance (Z^0) of the patients in this study was small (12.4 Ω); a normal value for supine patients is 22.5–24 Ω, that in the presence of pulmonary oedema, 18 Ω [32]. The small value we attribute to non-cardiogenic pulmonary oedema (adult respiratory distress syndrome) and pulmonary atelectasis, which alter the air–fluid relationships in the lungs and hence the lung resistivity. A reduction in thoracic bioimpedance has been noted with pleural effusion, and an increase with pneumothorax, dehydration and chronic obstructive lung disease [33], which would support this hypothesis, and in general the patients with more severe lung infiltrates on chest radiographs had smaller Z^0 values. Alternatively, as Bernstein [5] has suggested, the reduced Z^0 in sepsis may be caused by muscle and cutaneous vasodilatation. The value of thoracic bioimpedance was not directly related to the difference or the ratio between the values for stroke volume from the two methods of measurement, as assessed by multiple linear regression. However, the maximum change in bioimpedance is scaled with the Z^0 value in the calculation of cardiac index by bioimpedance, and the small values of Z^0 in these patients may be outside the range over which the assumptions used in the bioimpedance technique are valid, and cause a non-linear error.

It has been suggested that, although the values for cardiac index do not agree with the values obtained with thermodilution, in any one patient the bioimpedance can monitor trends in cardiac output [31]. The rationale for this is that each individual patient has a different relationship between cardiac index measured by thermodilution and bioimpedance, with a different gradient and offset to the regression line, and reasonably low limits of agreement. When results are pooled, as in this study, the resulting pooled limits of agreement are much worse than the individual values. For individual patients, the limits of agreement were between ± 0.29 and ± 2.55 litre $\text{min}^{-1}\,\text{m}^{-2}$ around the bias values, the average limits of agreement were ± 1.2 litre $\text{min}^{-1}\,\text{m}^{-2}$. Thus on average, even in an individual patient, to be 95 % certain that one value of cardiac output is significantly different from another measured by bioimpedance, the difference between the two readings has to be greater than 1.2 litre $\text{min}^{-1}\,\text{m}^{-2}$. Thus, even as a monitor of changes in cardiac index in individual septic patients, the bioimpedance technique is too insensitive for clinical use. It might be of value if the patients with low limits of agreement could be identified, but this is not possible.

A significant proportion of the thoracic bioimpedance change during systole may arise because of changes in the blood volume of the lungs [1, 34]. If the change in thoracic bioimpedance that occurs in systole is caused by an increase in pulmonary blood volume by a volume equivalent to the right ventricular stroke volume, then the stroke volume might be expected to be related to the change in bioimpedance during systole, δZ, and not its maximum first derivative $\delta Z/\delta t\text{max}$. This, however, does not occur; blood also leaves the lungs during systole and so the maximum rate of change of bioimpedance, $\delta Z/\delta t\text{max}$, is used. This represents the maximum rate of increase in blood volume (i.e. flow) in the lungs and occurs in early systole when the majority of the incoming pulmonary blood flow would be expected to expand capacitance vessels and remain within the lung. By extrapolating this flow over the whole of systole, a value for stroke volume is obtained. In septic patients requiring artificial ventilation, pulmonary hypertension is an almost universal finding, and pulmonary haemodynamics are markedly altered. Thus the relationship between $\delta Z/\delta t\text{max}$ and overall stroke volume may not remain the same, and so the extrapolations used in the thoracic bioimpedance method to calculate the cardiac index may fail.

There is also a more fundamental reason why the bioimpedance method does not measure cardiac index in the septic patient. The method relies on the oversimplified assumption that the thorax is a homogeneous conductor, shaped like a truncated cone. The change in impedance between the top and bottom of the thorax is attributed to changes in the blood content of the thorax. The impedance *decreases* during systole, implying that the thoracic blood volume *increases* during systole. This is physiologically unlikely; the change in impedance is probably caused by redistribution of blood within the thorax, which is thus not acting as a homogeneous conductor, and so the central theory of the method is suspect. Therefore, although the method works with normal subjects, if the underlying theory is unsound there is no reason why it should work in all circumstances.

ACKNOWLEDGEMENTS

The authors thank Drs Sear and Foëx for the loan of the NCCOM-3. Dr Young was a Medical Research Council Research Training Fellow during the study; Dr McQuillan was funded by the Chest, Heart and Stroke Association.

REFERENCES

1. Bonjor FH, van den Berg JW, Dirken MN. The origin of the variations in body impedance occurring during the cardiac cycle. *Circulation* 1952; **6**: 415–420.

2. Nyboer J. *Electrical Impedance Plethysmography*. Springfield, Illinois: CC Thomas Co., 1959.
3. Kubicek WG, Karnegis JN, Patterson RP, Witsoe DA, Mattson RH. Development and evaluation of an impedance cardiac output system. *Aerospace Medicine* 1966; **37**: 1208–1212.
4. Kubicek WG, Patterson RP, Witsoe DA. Impedance cardiography as a non-invasive method to monitor cardiac function and other parameters of the cardiovascular system. *Annals of the New York Academy of Science* 1970; **170**: 734–732.
5. Bernstein DP. A new stroke volume equation for thoracic electrical bioimpedance: theory and rationale. *Critical Care Medicine* 1986; **14**: 904–909.
6. Bone RC, Let's agree on terminology: definitions of sepsis. *Critical Care Medicine* 1991; **19**: 973–976.
7. Masaki DI, Greenspoon JS, Ouzounian JG. Noninvasive determination of cardiac output by thoracic electrical bioimpedance. *Critical Care Medicine* 1990; **18**: 121–122.
8. Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet* 1986: 307–310.
9. Weissler AM, Garrard CL jr. Systolic time intervals in cardiac disease (1). *Modern Concepts in Cardiovascular Disease* 1971; **40**: 1–4.
10. Ebert TJ, Eckberg DL, Vetrovec GM, Cowley MJ. Impedance cardiograms reliably estimate beat-by-beat changes in left ventricular stroke volume in humans. *Cardiovascular Research* 1984; **18**: 354–360.
11. Aust PE, Belz GG, Belz G, Koch W. Comparison of impedance cardiography and echocardiography for measurement of stroke volume. *European Journal of Clinical Pharmacology* 1982; **23**: 475–477.
12. Northridge D, Findlay IN, Wilson J, Henderson E, Dargie HJ. Non-invasive determination of cardiac output by Doppler echocardiography and electrical bioimpedance. *British Heart Journal* 1990; **63**: 93–97.
13. Teo KK, Hetherington MD, Haennel RG, Greenwood PV, Rossall RE, Kappagoda T. Cardiac output measured by impedance cardiography during maximal exercise tests. *Cardiovascular Research* 1985; **19**: 737–743.
14. Saladin V, Zussa C, Risica G, Michielon P, Paccagnella A, Cipolotti G, Simini G. Comparison of cardiac output estimation by thoracic electrical bioimpedance, thermodilution, and Fick methods. *Critical Care Medicine* 1988; **16**: 1157–1158.
15. Naggar CZ, Dobnik DB, Flessas AP, Kripke BJ, Ryan TJ. Accuracy of stroke index as determined by the transthoracic electrical impedance method. *Anesthesiology* 1975; **42**: 201–205.
16. Edmunds AT, Godfrey S, Tooley M. Cardiac output measured by transthoracic impedance cardiography at rest, during exercise and at various lung volumes. *Clinical Science* 1982; **63**: 107–113.
17. Hatcher DD, Srb OD. Comparison of two noninvasive techniques for estimating cardiac output during exercise. *Journal of Applied Physiology* 1986; **61**: 155–159.
18. Smith SA, Russell AE, West MJ, Chalmers J. Automated non-invasive measurement of cardiac output: comparison of electrical bioimpedance and carbon dioxide rebreathing techniques. *British Heart Journal* 1988; **59**: 292–298.
19. Milsom I, Siversson R, Biber B, Olsson T. Measurement of stroke volume with impedance cardiography. *Clinical Physiology* 1982; **2**: 409–417.
20. Keim HJ, Wallace JM, Thurston H, Case DB, Drayer JIM, Laragh JH. Impedance cardiography for determination of stroke index. *Journal of Applied Physiology* 1976; **41**: 797–799.
21. Denniston JC, Maher JT, Reeves JT, Cruz JC, Cymerman A, Grover RF. Measurement of cardiac output by electrical impedance at rest and during exercise. *Journal of Applied Physiology* 1976; **40**: 91–95.
22. Milsom I, Forssman L, Biber B, Dottori O, Siversson R. Measurement of cardiac stroke volume during Cesarian section: a comparison between impedance cardiography and the dye dilution technique. *Acta Anaesthesiologica Scandinavica* 1983; **27**: 421–426.
23. Castor G, Molter G, Helms J, Niedermark I, Altmayer P. Determination of cardiac output during positive end-expiratory pressure—noninvasive electrical bioimpedance compared with standard thermodilution. *Critical Care Medicine* 1990; **18**: 544–546.
24. Gotshall RW, Wood VC, Miles DS. Comparison of two impedance cardiographic techniques for measuring cardiac output in critically ill patients. *Critical Care Medicine* 1989; **17**: 806–811.
25. Spinale FG, Reines D, Crawford FA. Comparison of bioimpedance and thermodilution methods for determining cardiac output: experimental and clinical studies. *Annals of Thoracic Surgery* 1988; **45**: 421–425.
26. Wong DH, Tremper KK, Stemmer EA, O'Connor D, Wilbur S, Zaccari J, Reeves C, Weidoff P, Trujillo RJ. Noninvasive cardiac output: simultaneous comparison of two different methods with thermodilution. *Anesthesiology* 1990; **72**: 784–792.
27. Bernstein DP. Continuous noninvasive real-time monitoring of stroke volume and cardiac output by thoracic electrical bioimpedance. *Critical Care Medicine* 1986; **14**: 898–901.
28. Appel PL, Kram HB, Mackabee J, Fleming AW, Shoemaker WC. Comparison of measurements of cardiac output by bioimpedance and thermodilution in severely ill surgical patients. *Critical Care Medicine* 1986; **14**: 933–935.
29. Donovan KD, Dobb GJ, Woods WPD, Hockings BE. Comparison of transthoracic electrical impedance and thermodilution methods for measuring cardiac output. *Critical Care Medicine* 1986; **14**: 1038–1044.
30. Preiser JC, Daper A, Parquier J-N, Contempre B, Vincent J-L. Transthoracic electrical bioimpedance versus thermodilution technique for cardiac output measurement during mechanical ventilation. *Intensive Care Medicine* 1989; **15**: 221–223.
31. Jewkes C, Sear JW, Verhoeff F, Sanders DJ, Foëx P. Non-invasive determination of cardiac output by thoracic electrical bioimpedance: a study of reproducibility and comparison with thermodilution. *British Journal of Anaesthesia* 1991; **67**: 788–794.
32. Fein A, Grossman RF, Jones JG, Goodman PC, Murray JF. Evaluation of transthoracic electrical impedance in the diagnosis of pulmonary oedema. *Circulation* 1979; **60**: 1156–1160.
33. Saunders CF. The use of transthoracic electrical bioimpedance in assessing thoracic fluid status in emergency department patients. *American Journal of Emergency Medicine* 1988; **6**: 337–340.
34. Patterson RP. Fundamentals of impedance cardiography. *IEEE Engineering in Medicine and Biology Magazine* 1989; March: 35–38.

British Journal of Anaesthesia 1993; 70: 63–69

DIFFERENTIAL EFFECTS OF ALFENTANIL, FENTANYL, PETHIDINE AND LIGNOCAINE ADMINISTERED INTRATHECALLY ON NOCICEPTIVE RESPONSES EVOKED BY LOW AND HIGH FREQUENCY STIMULATION OF SOMATIC NERVES

C. WANG, A. KOUTSOUKOU-DRITSOPOULOU, M. K. CHAKRABARTI, A. HOLDCROFT AND J. G. WHITWAM

SUMMARY

We have studied in anaesthetized dogs the effects of alfentanil, fentanyl, pethidine and lignocaine administered intrathecally on nociceptive responses evoked by low and high frequency supramaximal electrical stimulation of the tibial and radial nerves. Doses were selected to abolish both Aδ and C fibre somatosympathetic reflexes to single stimuli. Pethidine and lignocaine eliminated reflex pressor and heart rate responses to repeated single stimuli and almost completely abolished responses to train stimulation. The pressor response to single stimuli was abolished by fentanyl and reduced by alfentanil, but these drugs did not reduce significantly this response to train stimulation, suggesting a stimulation rate-dependent effect. Of the opioids, only pethidine had an effect comparable to that of lignocaine. The absence of sympathetic block and antagonism by naloxone imply a lack of significant local anaesthetic effect. We suggest that the greater analgesic efficacy of pethidine is a result of endogenous synergism between a minor local anaesthetic and a major opioid effect. (Br. J. Anaesth. 1993; **70**: 63–69)

KEY WORDS

Analgesics: alfentanil, fentanyl, pethidine. Anaesthetics, local: lignocaine. Anaesthetic techniques: spinal. Nerves: somatic, stimulation frequency. Reflexes: somatosympathetic.

Opioids and local anaesthetic drugs cause analgesia when applied to the spinal cord; however, the efficacy of opioids for the relief of acute pain in some circumstance (for example during surgical or obstetric procedures) is often inadequate compared with local anaesthetics [1, 2]. The addition of small concentrations of local anaesthetics to opioids may be used to improve the quality of pain relief [2, 3]. Differences in the efficacy of the analgesic response to opioids may relate to the type of stimulation which presents to the dorsal horn cells. It is known that acute pain is accompanied usually by sympathetic responses which have been used to measure pain by recording either sympathetic nerve activity or, for example, changes in arterial pressure. In contrast, pain without acute episodes may not be accompanied by overt sympathetic responses. The differences in the type of stimulation are either its origins or its severity, which would include intensity and the numbers and firing frequency of afferent fibres.

This study was undertaken to test if the frequency of stimulation can modulate the antinociceptive effects of alfentanil, fentanyl, pethidine and lignocaine. We chose two different types of afferent somatic stimuli. The first was a series of single electrical stimuli supramaximal for activation of both Aδ and C fibre-mediated responses at 0.33 Hz, and the second comprised stimuli of the same intensity applied as 10-s trains at 30 Hz.

MATERIALS AND METHODS

Investigations were carried out in 15 greyhound dogs weighing between 27.6 and 32.6 kg (approved under Home Office Licence No PPL 70/01654). Anaesthesia was induced with methohexitone 15 mg kg^{-1} i.v., the trachea was intubated and the lungs ventilated with oxygen enriched air. Anaesthesia was maintained using 1% α-chloralose in an initial bolus dose of 30 mg kg^{-1} i.v. followed by a continuous infusion of 17.5 mg kg^{-1} h^{-1} i.v. and muscle paralysis was maintained using suxamethonium 10 mg i.v. every 30 min. The left femoral artery and vein were cannulated for arterial pressure recording, blood sampling, drug administration and fluid infusion. Arterial pH was maintained in the range 7.30–7.35, Pa_{O_2} 20–27 kPa, Pa_{CO_2} 4.5–5.5 kPa and oesophageal temperature 37–39 °C.

A site for intrathecal (i.t.) drug injection was prepared by removal of the lamina of the 2nd and 3rd lumbar vertebrae, exposure of the dura mater and intradural cannulation with a 22-gauge Y-can. Lateral superficial branches of the radial and tibial

---

C. WANG, M.B.; A. KOUTSOUKOU-DRITSOPOULOU, MD.; M. K. CHAKRABARTI, B.SC., M.PHIL.; A. HOLDCROFT, M.B., CH.B., F.R.C.ANAES., M.D.; J. G. WHITWAM, M.B., CH.B., PH.D., F.R.C.P., F.R.C.ANAES.; Department of Anaesthetics, Hammersmith Hospital, Royal Postgraduate Medical School, Du Cane Road, London W12 0NN. Accepted for Publication: July 17, 1992.

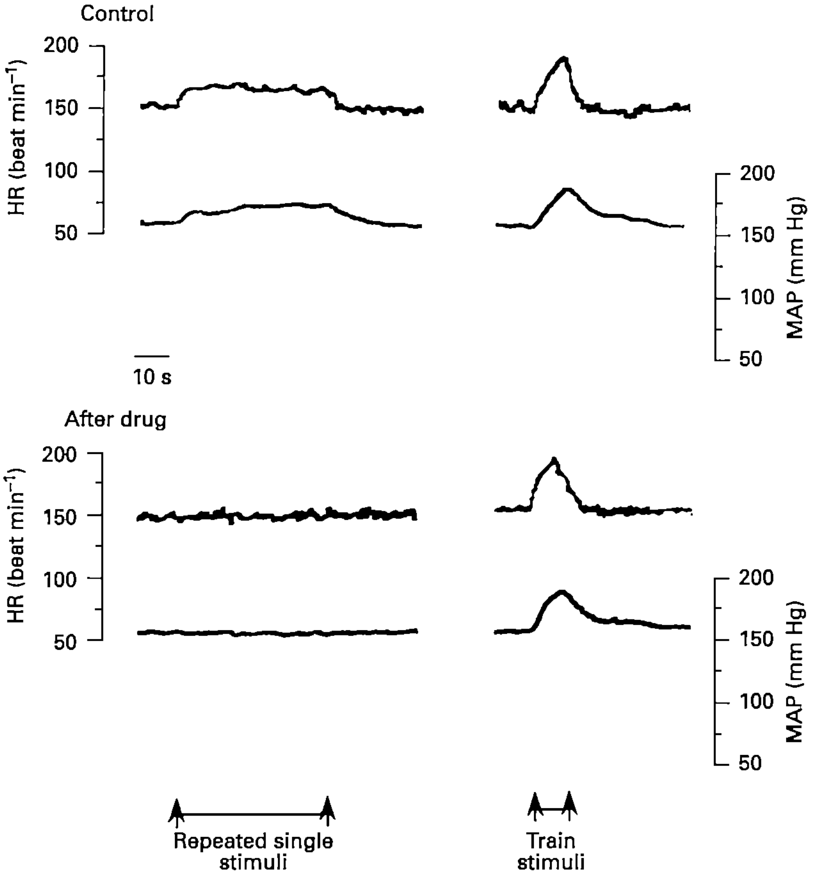


FIG. 1. Typical recording of reflex responses in the heart rate (HR) and mean arterial pressure (MAP) evoked by repeated single stimuli (0.33 Hz, 30 V, 0.5 ms) and a 10-s train of stimuli (30 Hz, 30 V, 0.5 ms) applied to the tibial nerve before (Control) and after fentanyl 0.15 mg i.t.

nerves were exposed in the left foreleg and right hind leg, respectively. Both nerves were desheathed, cut distally, immersed in mineral oil and mounted on silver electrodes. The renal sympathetic nerves were exposed retroperitoneally along the right renal artery. Single fascicles of nerve were desheathed, cut distally near the kidney, immersed in a mineral oil pool and mounted on silver–silver chloride electrodes. The preparation was maintained throughout in a lateral position with head up tilt of 15° to prevent ascending spread of intrathecal drugs.

The mean arterial pressure (MAP) was measured with a calibrated strain gauge and displayed together with the beat-by-beat heart rate (HR) using a heated stylus recording system (Devices M19).

Repeated single supramaximal electrical stimuli (frequency 0.33 Hz, intensity 30 V and duration 0.5 ms) and 10-s trains of high frequency stimuli (30 Hz, intensity 30 V and duration 0.5 ms) were applied to both the tibial and radial nerves using a Grass S88 stimulator with matched directly coupled isolation unit (Grass 478A). Efferent activity in renal sympathetic nerves was processed through a preamplifier (Tektronix type 122) and displayed on a dual-beam oscilloscope (Tektronix type 565). Average transients of the evoked sympathetic responses were obtained using a Neurolog system (NL750 Digitimer) and 16 responses were averaged on each occasion. The averaged responses were rectified and integrated (Neurolog NL90) and both signals were displayed on a pen recorder (Devices MX2).

After being set up, the preparation was allowed to stabilize for 30 min, when control data were obtained. To record the evoked responses in MAP and HR caused by repeated single stimuli, the stimulation was sustained for up to 1 min to allow development and stabilization of the maximal response in MAP and HR. The changes in MAP and HR evoked by repeated single and train stimuli were measured as the peak responses (fig. 1). The MAP and HR were then allowed to return to prestimulus control values. The evoked response in renal sympathetic nerves could not be recorded during train stimulation, as the repeated stimulus artefact interferes with and distorts the sympathetic signal.

The doses of alfentanil, fentanyl, pethidine and lignocaine were chosen to just abolish the evoked reflexes in renal sympathetic nerves to repeated single stimuli applied to the *tibial nerve* in a series of preparations. The doses for alfentanil 7.5 mg (5 mg ml^{-1}) and fentanyl 0.15 mg (0.05 mg ml^{-1}) had been determined in previous studies [4, 5]. In the

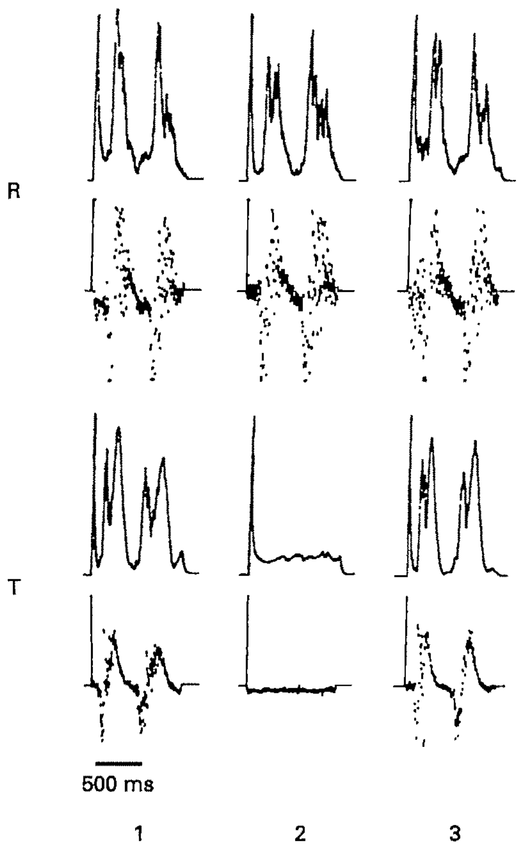


FIG. 2. Typical recording of the effects of pethidine administered i.t. followed by naloxone i.v. on the responses in a renal sympathetic nerve evoked by a single electrical stimulus (30 V, 0.5 ms duration, 0.33 Hz) applied to the tibial (T) and radial (R) nerves. Lower trace: average transient of 16 responses. Upper trace: rectified integral of averaged signal. 1 = Control; 2 = 5 min after pethidine 30 mg i.t.; 3 = 5 min after naloxone 2 mg i.v. It can be seen that pethidine did not affect the radial somato-sympathetic reflexes (upper traces) to any significant degree and that its effect on tibial nerve stimulation was antagonized completely by naloxone. This indicates that the action of pethidine is not primarily a local anaesthetic effect.

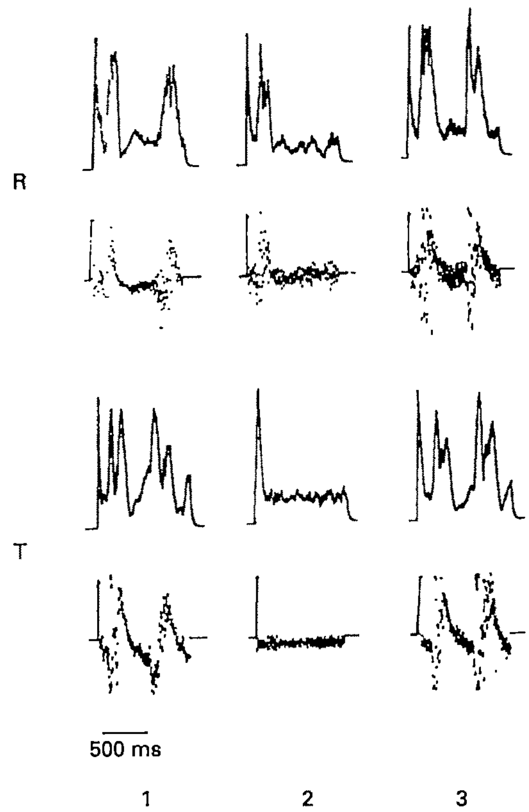


FIG. 3. Effects of alfentanil administered i.t. followed by naloxone i.v. on the responses in a renal sympathetic nerve evoked by a single electrical stimulus (30 V, 0.5 ms duration, 0.33 Hz) applied to the tibial (T) and radial (R) nerves. Lower trace: average transient of 16 responses. Upper trace: rectified integral of averaged signal. 1 = Control; 2 = 5 min after alfentanil 7.5 mg i.t.; 3 = 5 min after naloxone 2 mg i.v.

present study, preliminary observations showed that the doses of pethidine and lignocaine which just abolished the somatosympathetic reflexes were 30 mg (20 mg ml^{-1}) and 10 mg (10 mg ml^{-1}) i.t., respectively. Alfentanil, fentanyl and pethidine were administered in each of five preparations. Five minutes after each drug administration, averaged evoked responses in the renal sympathetic nerve to repeated single stimulation applied to the tibial nerve confirmed that the drug had abolished the sympathetic response. The reflexes evoked in renal sympathetic nerves by repeated single stimulation of the *radial nerve* were recorded to provide a control and to determine if there was a direct effect on the efferent sympathetic pathway. When a stable state was established, then either repeated single (0.33 Hz) or 10-s trains (30 Hz) of stimuli were applied in a random sequence. The study was then repeated with the repeated single and train stimuli in reversed order. Reflex responses in MAP and HR were recorded. When the study was completed, naloxone 2 mg i.v. was administered. When the evoked reflexes in renal sympathetic nerves, MAP and HR returned to values similar to control, the sequence described above was repeated to confirm that the preparation had returned to its control state. Lignocaine 10 mg (10 mg ml^{-1}) was then injected i.t. in all preparations and a similar random series of stimulations and measurements was repeated. The duration of these experiments varied between 7 and 9 h.

Statistical analysis was performed with analysis of variance, where appropriate, followed by paired Student's *t* tests.

RESULTS

Somatosympathetic reflexes

Tibial nerve stimulation. Alfentanil 7.5 mg, fentanyl 0.15 mg, pethidine 30 mg and lignocaine 10 mg administered i.t. abolished both the Aδ and C reflexes in the renal sympathetic nerves evoked by single stimuli applied to the tibial nerves of all the dogs (figs 2–4).

Radial nerve stimulation. The somatosympathetic reflexes evoked by radial nerve stimulation were unaffected by fentanyl and pethidine (fig. 2). In contrast, in preparations receiving alfentanil, whereas the Aδ fibre-mediated reflexes in renal sympathetic nerves did not change significantly, the C fibre-mediated longer latency reflex was abolished, suggesting either systemic absorption or supraspinal spread (fig. 3) [4]. Lignocaine i.t. completely abolished the reflexes in renal sympathetic nerves to both tibial and radial nerve stimulation (fig. 4), because it blocks the efferent sympathetic nerves.

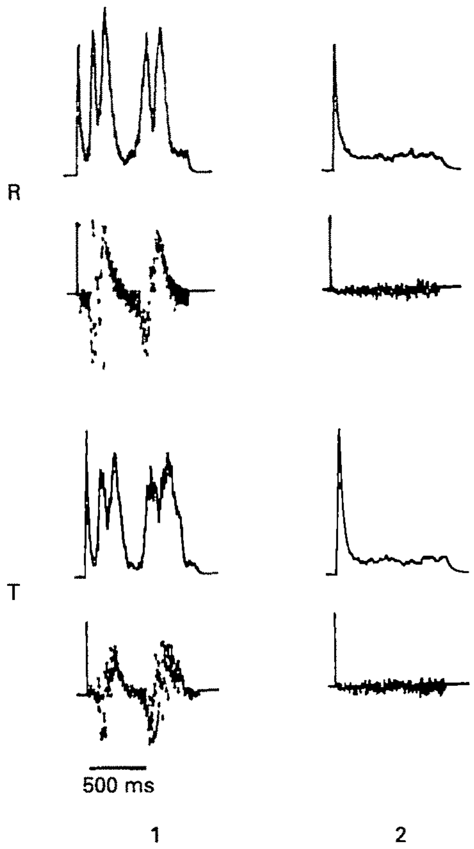


FIG. 4. Effects of lignocaine administered i.t. on the evoked responses in a renal sympathetic nerve by a single electrical stimulus (30 V, 0.5 ms duration, 0.33 Hz) applied to the tibial (T) and radial (R) nerves. Lower trace: average transient of 16 responses. Upper trace: rectified integral of averaged signal. 1 = Control; 2 = 5 min after lignocaine 10 mg i.t.

Arterial pressure and heart rate

Tibial nerve stimulation. It may be seen that the increase in MAP caused by repeated single stimulation of the tibial nerve was eliminated by fentanyl, pethidine and lignocaine, and markedly reduced by alfentanil (table I; figs 1, 5). The increase in MAP induced by trains of high frequency stimulation of the tibial nerve was abolished completely by lignocaine and only a very small residual pressor response remained in preparations receiving pethidine (fig. 5). In contrast, after fentanyl and alfentanil, the evoked increase in MAP caused by high frequency train stimulation was slightly greater than control (ns). The reflex increase in HR during single stimulation of the tibial nerve was abolished completely by fentanyl, lignocaine and pethidine (table I; figs 1, 6); after alfentanil an increase in HR of 6.4% was not significantly different from the control value of 7.7%. The responses to trains of stimuli were more variable. For example, there was a significant increase in the heart rate response after alfentanil from 15% to 54.3%. In contrast, after fentanyl the increase in HR caused by trains of stimuli remained almost unchanged compared with the control responses, and this response was abolished by both pethidine and lignocaine.

Radial nerve stimulation. The reflex increases in MAP and HR caused by either repeated single or train stimulation of the radial nerve were similar to control values after alfentanil and fentanyl. While this was also true for MAP with pethidine (table I), the response in HR to low frequency stimulation was reduced. However, in the group receiving pethidine there was an increase in resting mean heart rate of 9 beat min^{-1} after i.t. administration (table I) (ns). This could explain this phenomenon, as, during train stimulation, a larger sympathetic response occurred which increased the HR to a mean value of 201 beat min^{-1},—a mean increase of 39 beat min^{-1} in the pethidine group compared with an increase in HR in the fentanyl group of 34 beat min^{-1} (table I). Lignocaine i.t. caused a small but statistically non-significant reduction in the reflex increases in MAP and HR in response to both low and high frequency stimulation (table I).

DISCUSSION

High strength electrical stimulation of somatic nerves causes reflex responses in the autonomic nervous system which are manifest, for example, by changes in arterial pressure [6, 7]. Directly recorded sympathetic nerve responses to single electrical stimuli applied to a somatic nerve show two bursts of activity mediated by afferent Aδ and C fibres [8, 9]. In this study the doses of alfentanil, fentanyl, pethidine and lignocaine used were the minimal required to just eliminate both the Aδ and C fibre-mediated responses evoked in renal sympathetic nerves to repeated single supramaximal electrical stimuli applied to the tibial nerve. The increase in MAP in response to repeated single stimulation was also abolished completely by fentanyl, pethidine and lignocaine. A large dose of alfentanil was required to abolish the Aδ reflex, with evidence of baroreflex sensitization causing a significant reduction in both MAP and HR ($P < 0.05$) (table I, fig. 3) and a small arterial pressure response persisted (fig. 5). This confirms previous observations which also indicated that the elimination of the tibial Aδ fibre-mediated reflex after alfentanil required a dose which had more general central effects, resulting either from systemic absorption or from supraspinal spread [4].

During high frequency train stimulation with the same stimulus intensity, the reflex increase in MAP was abolished almost completely by pethidine and abolished completely by lignocaine. In contrast, the evoked increases in MAP did not change significantly from control values after both alfentanil and fentanyl; this suggests that the antinociceptive effect of these opioids is dependent on the frequency of stimulation. Thus a dose which abolishes the effect of low frequency afferent stimulation does not necessarily provide adequate "analgesia" at higher frequencies of stimulation even when its duration is relatively short—10 s in the present study. This phenomenon could be one factor explaining the relative ineffectiveness of the opioids, compared with local anaesthetic drugs, in relieving severe intra-operative pain.

A further increase in the intrathecal dose of fentanyl could possibly cause depression of the nociceptive response in arterial pressure evoked by high frequency stimulation. However, this may not

TABLE I. *Mean (SD) mean arterial pressure (MAP) and heart rate (HR) from non-stimulation control values (resting), repeated single stimulation (0.33 Hz, 30 V, duration 0.5 ms) and 10-s train of stimulation (30 Hz, 30 V, duration 0.5 ms) applied to the tibial and radial nerves before and after drug treatment.* $P < 0.05$: ** compared with non-stimulation either during control or after drug administration; † compared with non-stimulated control values before and after drug administration, indicating a degree of baroreceptor sensitization in the alfentanil group*

		Tibial nerve		Radial nerve	
	Resting	Single	Train	Single	Train
Control					
Alfentanil 7.5 mg i.t. ($n = 5$)					
MAP (mm Hg)	154 (7)	168 (8)*	184 (7)*	170 (6)*	189 (4)*
HR (beat min^{-1})	148 (10)	160 (9)*	171 (13)*	163 (16)*	180 (9)*
Fentanyl 0.15 mg i.t. ($n = 5$)					
MAP (mm Hg)	154 (7)	168 (8)*	184 (7)*	170 (6)*	189 (4)*
HR (beat min^{-1})	146 (13)	161 (15)*	171 (15)*	162 (13)*	177 (21)*
Pethidine 30 mg i.t. ($n = 5$)					
MAP (mm Hg)	165 (13)	179 (14)*	195 (16)*	185 (22)*	197 (24)*
HR (beat min^{-1})	153 (15)	170 (9)*	176 (12)*	172 (13)*	185 (13)*
Lignocaine 10 mg i.t. ($n = 15$)					
MAP (mm Hg)	164 (11)	179 (13)*	198 (24)*	183 (12)*	198 (20)*
HR (beat min^{-1})	153 (12)	168 (15)*	179 (20)*	171 (11)*	186 (14)*
After drug					
Alfentanil 7.5 mg i.t. ($n = 5$)					
MAP (mm Hg)	118 (16)†	121 (15)	146 (17)*	130 (18)*	153 (20)*
HR (beat min^{-1})	80 (13)†	85 (13)	122 (12)*	90 (13)*	130 (22)*
Fentanyl 0.15 mg i.t. ($n = 5$)					
MAP (mm Hg)	152 (15)	152 (15)	181 (25)*	172 (13)*	183 (13)*
HR (beat min^{-1})	138 (17)	138 (17)	166 (25)*	153 (15)*	172 (15)*
Pethidine 30 mg i.t. ($n = 5$)					
MAP (mm Hg)	158 (10)	158 (10)	161 (17)	177 (15)*	190 (23)*
HR (beat min^{-1})	162 (6)	159 (7)	152 (8)	168 (24)	201 (18)*
Lignocaine 10 mg i.t. ($n = 15$)					
MAP (mm Hg)	161 (8)	161 (8)	161 (8)	171 (7)*	186 (7)*
HR (beat min^{-1})	149 (13)	149 (13)	149 (13)	162 (12)*	174 (11)*

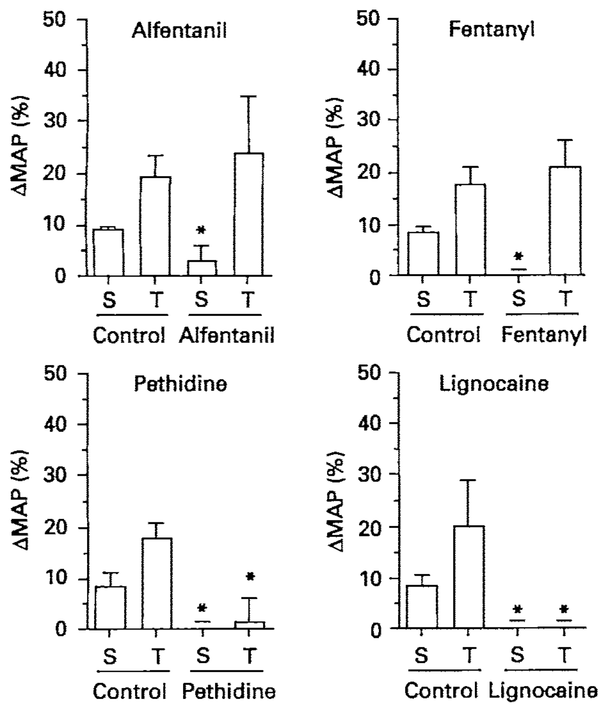


FIG. 5. Percentage increase (mean, SD) in mean arterial pressure (MAP) from non-stimulation control evoked by repeated single stimulation (S) and 10-s train stimulation (T) applied to the tibial nerve before and after alfentanil 7.5 mg ($n = 5$), fentanyl 0.15 mg ($n = 5$), pethidine 30 mg ($n = 5$) and lignocaine 10 mg ($n = 15$), administered i.t. $*P < 0.05$ compared with control.

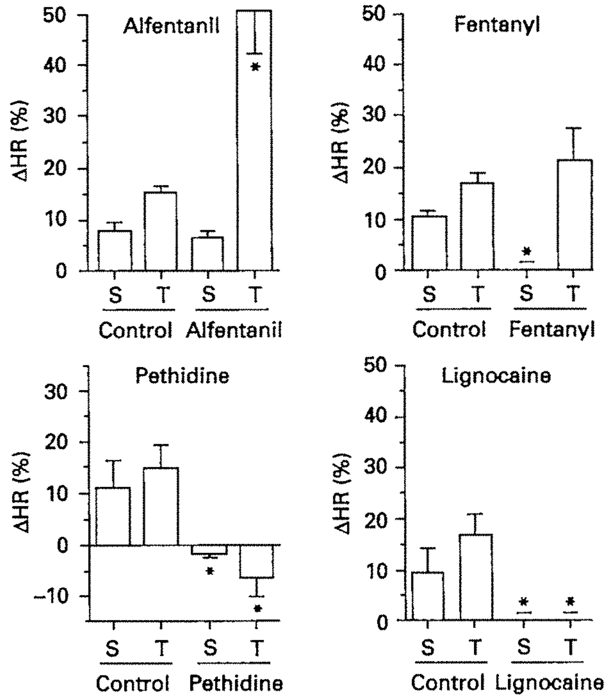


FIG. 6. Percentage increase (mean, SD) in heart rate (HR) from non-stimulation control evoked by a repeated single stimulation (S) and 10-s train tetanic stimulation (T) applied to the tibial nerve before and after alfentanil 7.5 mg ($n = 5$), fentanyl 0.15 mg ($n = 5$), pethidine 30 mg ($n = 5$) and lignocaine 10 mg ($n = 15$), administered i.t. $*P < 0.05$ compared with control.

occur with alfentanil, because the dose used in these experiments was very large—7.5 mg i.t., with evidence of cardiovascular effects related to either systemic absorption or supraspinal diffusion. In addition, the depression and abolition of the reflex nociceptive cardiovascular response to train stimuli may not be achieved even when the dose of fentanyl is increased to a very high concentration. It is reported that the effectiveness of spinal opioids in providing further analgesia in man does not always occur with an increase in dose beyond an adequate level of analgesia [2]. The dose of fentanyl administered in this study was greater than that used usually in clinical practice [2]. Moreover, the potential risk of respiratory depression is also increased when larger doses of opioids are used.

The site of action of spinally applied opioids is in the dorsal horn [10, 11] and fentanyl, alfentanil and pethidine act via mu opioid receptors which involve potassium channels [12], whereas local anaesthetic drugs act predominantly on the sodium channels in axonal membranes [13]. There is evidence that the effect of local anaesthetics may differ on sympathetic, sensory and motor fibres [14]. Cousins [13] suggested that block of primary afferent transmission is a more potent method of producing pain relief than local inhibition in the spinal cord—a view based on evidence from clinical pain studies with spinally applied opioids and local anaesthetics.

Pethidine was introduced in 1939 [15]. In 1946, Way [16] showed that it could produce corneal analgesia, sciatic nerve block and intradermal analgesia, suggesting that it was a local anaesthetic. Until the present study, this was the basis of the explanation for its superiority over other opioids as an analgesic drug when applied topically [2, 17]. However, in this study pethidine had an effect similar to that of lignocaine on the reflex increase in MAP in response to both repeated single and train stimulation applied to the tibial nerve. This could be interpreted as a local anaesthetic effect but there was no evidence for this, as its effects were antagonized completely by naloxone (fig. 2). Also, comparison of the effects of pethidine and lignocaine on the somatosympathetic responses evoked by radial nerve stimulation showed that, while pethidine (fig. 2) blocked the afferent pathway, there was no evidence of efferent sympathetic block. This contrasts with lignocaine, which blocked both the efferent sympathetic and afferent nociceptive pathways (fig. 4). The increase in MAP evoked by both single and train stimulation of the radial nerve was reduced slightly after lignocaine, compared with pethidine, which would be compatible with limited local block of the efferent sympathetic system.

Pain relief in labour following extradural opioids has been disappointing and the addition of bupivacaine is recommended [18–20]. However, i.t. pethidine has been used successfully in labour [21] and for Caesarean section [22, 23]. It has provided satisfactory saddle block for perineal surgery [24], and it has been used for prostatic surgery [25]. It has also been reported that, after major abdominal surgery, a combination of extradural morphine and local anaesthetic provided better analgesia than morphine alone [3] and there is synergism between morphine and lignocaine [26]. Synergism between this putative local anaesthetic property and the major opioid action, observed in the present study, could explain its greater effectiveness compared with fentanyl and alfentanil. For example, a combination of 0.0625 % bupivacaine and 0.0002 % fentanyl has been shown to produce analgesia in labour [27].

Another possible explanation for the effectiveness of pethidine is that it could, conceivably, act at kappa receptors, in addition to mu receptors, in the spinal cord. Kappa receptors account for more than 50 % of opioid receptors in the human spinal cord [28]. The kappa receptor may also predominate in some other higher mammalian species [29].

In conclusion, this study shows that an intrathecal dose of opioids which causes a reduction in the reflex sympathetic and cardiovascular responses to repeated single nociceptive stimuli may not depress such reflexes to stimulation of the same intensity but at a greater frequency. It provides a hypothesis for one contributory factor to the observation of the relative ineffectiveness of opioid analgesia in many clinical situations. It also shows that pethidine is a more effective "analgesic" drug than either fentanyl or alfentanil. It does not cause measurable block of efferent sympathetic activity, which could be an advantage compared with lignocaine. The fact that its effects are antagonized by naloxone allow a further intriguing hypothesis that a single drug, pethidine, may provide endogenous synergism between a small local anaesthetic effect and a major opioid action, which would explain or reconcile many previous experimental and clinical observations.

REFERENCES

1. Cousins MJ, Mather LE. Intrathecal and epidural administration of opioids. *Anesthesiology* 1984; **61**: 276–310.
2. De Castro J, Meynadier J, Zenz M. *Regional Opioid Analgesia: Physiopharmacological Basis, Drugs, Equipment and Clinical Application.* Dordrecht: Kluwer Academic Publishers, 1991.
3. Rawal N. Indications for the use of intraspinal opioids. In: Rawal N, Coombs DW, eds. *Spinal Narcotics.* Dordrecht: Kluwer Academic Publishers, 1990; 43–61.
4. Wang C, Chakrabarti MK, Whitwam JG. Effect of low and high concentrations of alfentanil administered intrathecally on Aδ and C fibre mediated somatosympathetic reflexes. *British Journal of Anaesthesia* 1992; **68**: 503–507.
5. Wang C, Chakrabarti MK, Galletly DC, Whitwam JG. Relative effects of intrathecal administration of fentanyl and midazolam on Aδ and C fibre reflexes. *Neuropharmacology* 1992; **31**: 439–444.
6. Gordon G. The mechanism of the vasomotor reflexes produced by stimulating mammalian sensory nerves. *Journal of Physiology (London)* 1943; **102**: 95–107.
7. Johansson B. Circulatory responses to stimulation of somatic afferents. *Acta Physiologica Scandinavica* 1962; (Suppl. 198): 1–91.
8. Sato A, Schmidt RF. Somatosympathetic reflexes: afferent fibres, central pathways, discharge characteristics. *Physiological Reviews* 1973; **37**: 916–947.
9. Whitman JG, Kidd C, Fussey IV. Responses in sympathetic nerves of the dog evoked by stimulation of somatic nerves. *Brain Research* 1979; **165**: 219–233.
10. Hammond DL. Intrathecal administration: methodological

considerations. In: Field HL, Besson JM, eds. *Progress in Brain Research*, Vol. 77. Amsterdam: Elsevier Science Publishers, 1988; 313–320.

11. Nishio Y, Sinatra RS, Kitahata LM, Collins JG. Spinal cord distribution of ^{3}H-morphine after intrathecal administration: relationship to analgesia. *Anesthesia and Analgesia* 1989; **69**: 323–327.
12. Dickenson AH. Mechanisms of the analgesic actions of opiates and opioids. *British Medical Bulletin* 1991; **47**: 690–702.
13. Cousins MJ. The spinal route of analgesia for acute and chronic pain. In: Dubner R, Gebhart GF, Bond MR, eds. *Proceedings of the Vth World Congress on Pain*. Amsterdam: Elsevier Science Publishers, 1988; 454–471.
14. Cousins MJ, Bromage PR. Epidural neural block. In: Cousins MJ, Bridenbaugh PO, eds. *Neural Blockade in Clinical Anesthesia and Management of Pain*. Philadelphia: J. B. Lippincott Company, 1988; 253–360.
15. Jaffe JH, Martin WR. Opioid analgesics and antagonists. In: Gilman AG, Goodman LS, Rall TW, Murad F, eds. *Goodman and Gilman's The Pharmacological Basis of Therapeutics*. New York: MacMillan Publishing Company, 1985; 491–531.
16. Way EL. Studies on the local anesthetic properties of isonipecaine. *Journal American Pharmacology Association* 1946; **35**: 44–47.
17. Sangerlangkarn S, Klaewtanong V, Jonglerttrakool P, Khankaew V. Merepidine as a spinal anesthetic agent: a comparison with lidocaine–glucose. *Anesthesia and Analgesia* 1987; **66**: 235–240.
18. Baraka A, Maktabi M, Noueihid R. Epidural meperidine–bupivacaine for obstetric analgesia. *Anesthesia and Analgesia* 1982; **61**: 652–656.
19. Justins DM, Francis D, Houlton PG, Reynolds R. A controlled trial of extradural fentanyl in labour. *British Journal of Anaesthesia* 1982; **54**: 409–414.
20. Cohen SE, Tan S, Albright GA, Halpern J. Epidural fentanyl/bupivacaine combinations for labor analgesia: effect of varying dosage. *Anesthesiology* 1986; **65**: A368.
21. Johnson MD, Hurley RJ, Gilbertson LI, Datta S. Continuous microcatheter spinal anesthesia with subarachnoid meperidine for labor and delivery. *Anesthesia and Analgesia* 1990; **70**: 658–661.
22. Boreen S, Leighton BL, Kent H, Norris MC. Intrathecal meperidine for labour analgesia: preliminary communication. *International Journal of Obstetric Anaesthesia* 1992; **1**: 149–155.
23. Camann WR, Bader AM. Spinal anaesthesia for Caesarean delivery with meperidine as the sole agent. *International Journal of Obstetric Anaesthesia* 1992; **1**: 156–158.
24. Acalovschi I, Ene V, Lörinczi E, Nicolaus F. Saddle block with pethidine for perineal operations. *British Journal of Anaesthesia* 1986; **58**: 1012–1016.
25. Lewis RP, Spiers SPW, McLaren IM, Hunt PCW, Smith HS. Pethidine as a spinal anaesthetic agent—a comparison with plain bupivacaine in patients undergoing transurethral resection of the prostate. *European Journal of Anaesthesiology* 1992; **9**: 105–109.
26. Fraser HM, Chapman V, Dickenson AH. Spinal local anaesthetic actions on afferent evoked responses and wind-up of nociceptive neurones in the rat spinal cord: combination with morphine produces marked potentiation of antinociception. *Pain* 1992; **49**: 33–41.
27. Chestnut DV, Laszewski LJ, Pollack KL, Bates JN, Manago NK, Choi WW. Continuous epidural infusion of 0.0625% bupivacaine-0.0002% fentanyl during the second stage of labor. *Anesthesiology* 1990; **72**: 613–618.
28. Czlonkowski A, Costa T, Przewlocki R, Pasi A, Herz A. Opiate receptor binding sites in human spinal cord. *Brain Research* 1983; **267**: 392–396.
29. Yaksh TL, Noueihed R. The physiology and pharmacology of spinal opiates. *Annual Review of Pharmacology and Toxicology* 1985; **25**: 433–462.

British Journal of Anaesthesia 1993; **70**: 70–75

GENETIC LINKAGE ANALYSIS OF CHROMOSOME 19 MARKERS IN MALIGNANT HYPERTHERMIA

S. P. BALL, H. R. DORKINS, F. R. ELLIS, J. L. HALL, P. J. HALSALL, P. M. HOPKINS, R. F. MUELLER AND A. D. STEWART

SUMMARY

Previous studies have reported that malignant hyperthermia susceptibility is caused in some families by inherited variation in a gene located on the short arm of chromosome 19 near to, or identical with, the ryanodine receptor gene (RYR1); this is expressed in skeletal muscle as a calcium release channel of the sarcoplasm reticulum. In other families, a gene in this location is excluded, but the locations of the genes involved have not yet been defined. We have analysed DNA samples from members of three large British families in whom in vitro *muscle contracture tests for malignant hyperthermia susceptibility have been carried out in accordance with the procedure recommended by the European Malignant Hyperthermia Group. The results presented here strongly suggest that the gene for malignant hyperthermia susceptibility in one or more of these three British families is located in the same region of chromosome 19q, although further work is required to decide whether or not the RYR1 gene itself is causative in these families. As genetic heterogeneity could not be excluded, we cannot yet recommend the use of DNA markers to replace* in vitro *contracture tests in the diagnosis of malignant hyperthermia susceptibility.* (Br. J. Anaesth. 1993; **70**: 70–75)

KEY WORDS
Genetic factors: linkage analysis. Hyperthermia: malignant.

Malignant hyperthermia (MH) is an inherited pharmacogenetic disorder characterized by muscle rigidity and accelerated metabolism, together with associated secondary manifestations in susceptible individuals exposed to triggering agents such as inhalation anaesthetics and depolarizing muscle relaxants [1]. Denborough and co-workers [2] described a pedigree in which clinical MH segregated in an autosomal dominant manner. Development of *in vitro* contracture testing to determine susceptibility to MH [3, 4] has permitted the screening of relatives of probands presenting with clinical MH. Susceptibility is determined currently by the contracture response of living muscle tissue to *in vitro* exposure to halothane and, separately, to caffeine. From 1984, the standard method for these tests is described in the procedure recommended by the European Malignant Hyperthermia Group [5]. This designates patients to be MHS (susceptible), MHE (equivocal) and MHN (normal) according to whether they respond abnormally to both drugs, one drug alone, or neither drug, respectively. Before 1984, patients were characterized as either positive or negative for malignant hyperthermia susceptibility. These family studies have confirmed the autosomal dominant mode of inheritance of MH susceptibility [6, 7]. Recent developments in molecular genetics should enable the mapping of gene(s) responsible for the disorder. This might in turn result in non-invasive methods for the presymptomatic diagnosis of MH susceptibility.

In certain breeds of pig, a similar (but perhaps not identical) disorder has been described [8]. The porcine gene conferring halothane-induced MH susceptibility, *HAL*, is genetically linked to those encoding glucose phosphate isomerase, *GPI*, and the ryanodine receptor, *RYR1* [9, 10], and is probably identical to the last. The human homologues of these loci are linked and lie on the long arm of chromosome 19, known as 19q [11].

We have studied three large British families segregating for MH susceptibility to see if a mutated gene on chromosome 19q may underlie this condition.

METHODS

Families

Patients are referred to the Leeds MH Investigation Unit after a suspected MH anaesthetic reaction. If the proband has survived and is found to be susceptible to malignant hyperthermia, other close relatives are invited to have a diagnostic muscle biopsy. If the proband has died, family studies are initiated with the parents, if possible.

S. P. Ball, ph.d., Washington Singer Laboratories, School of Biological Sciences, University of Exeter, Exeter. H. R. Dorkins, m.b., b.s., m.r.c.p., St Peter's College, Oxford. F. R. Ellis, ph.d., f.r.c.anaes.; P. J. Halsall, m.b., ch.b.; P. M. Hopkins, m.b., b.s., f.r.c.anaes.; Malignant Hyperthermia Investigation Unit, Department of Clinical Medicine (Anaesthesia), St James's University Hospital, The University of Leeds, Leeds LS9 7TF. J. L. Hall, b.sc.; R. F. Mueller, m.r.c.p.; A. D. Stewart, ph.d.; Yorkshire Regional DNA Laboratory, Department of Genetics, The University of Leeds, Leeds. Accepted for Publication: July 17, 1992.

Correspondence to F.R.E.

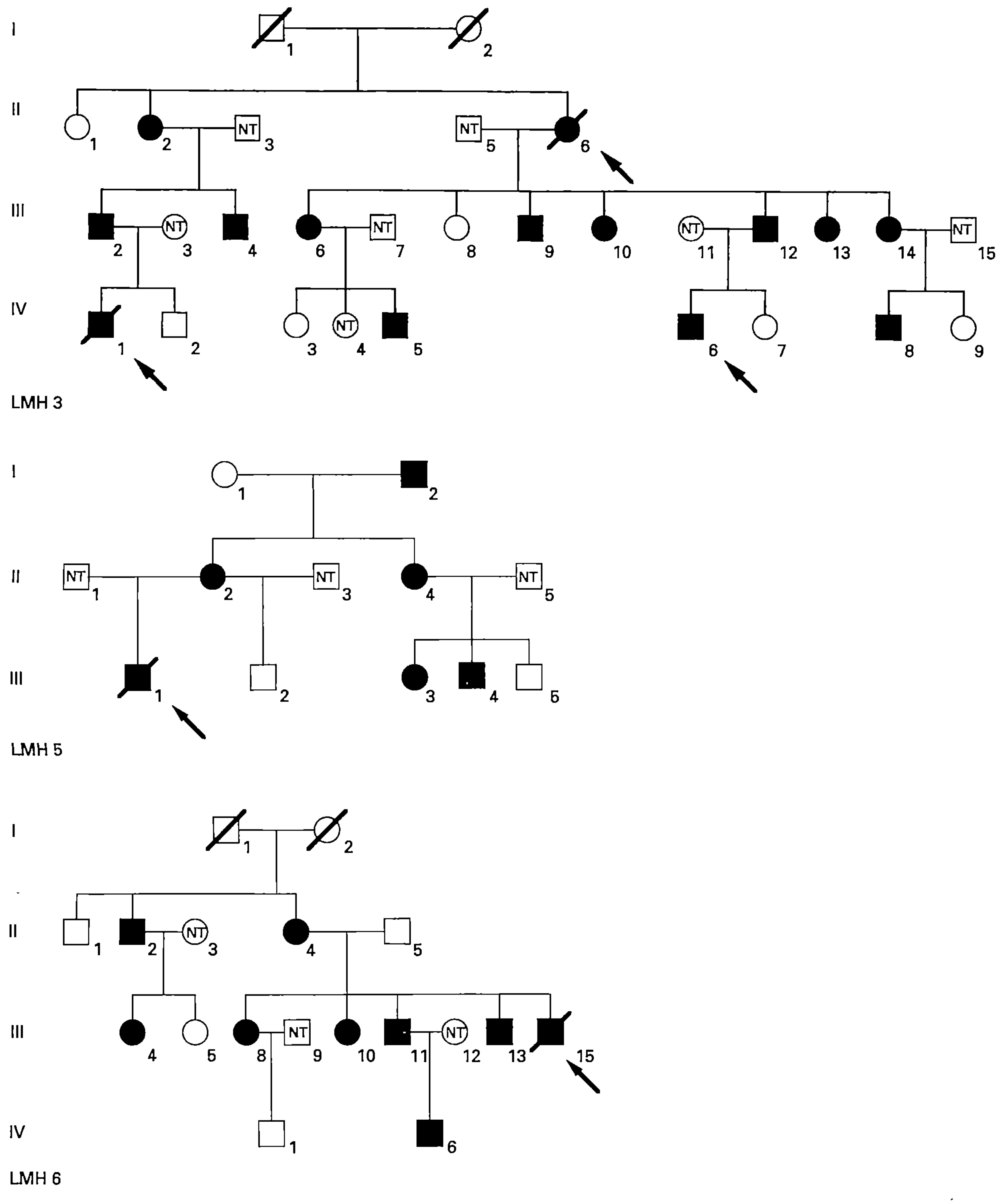


FIG. 1. Pedigrees of three families used for the linkage analysis of susceptibility to malignant hyperthermia. ● = *In vitro* contracture test (IVCT) positive—that is, MHS; ○ = IVCT negative (MHN); NT = not tested with IVCT.

Blood was collected from members of three, large triple-generation families (LMH3, LMH5 and LMH6) which had been studied in this way. The pedigrees of these families are shown in figure 1. These families were selected because at least one member of each had had an episode of fulminant MH, and because the *in vitro* contracture tests in the family members gave results which permit definite diagnosis. In two of these families, the proband had died from MH; in the other family, there were two probands, one of whom died and the other survived.

DNA was extracted from peripheral blood samples using standard methods [12]. Typing of alleles at genetic marker loci was performed as described below, using Southern blotting and microsatellite amplification procedures. The results from these genetic typings were used for linkage analysis.

Southern blot analysis

Southern blots of genomic DNA digested with the appropriate restriction enzyme were hybridized with DNA probes to reveal the restriction fragment length

TABLE I. *DNA probes detecting restriction fragment length polymorphisms (RFLP) used in this investigation*

Locus name	Locus symbol	Probe name	Enzyme detecting RFLP	Allele size	Allele frequency
D19S7	D19S7	p4.1	MspI	9.0	0.32
				8.0	0.68
Apolipo-protein CII	APOC2	cDNA NJ 3.6	TaqI	3.8	0.58
				3.5	0.44

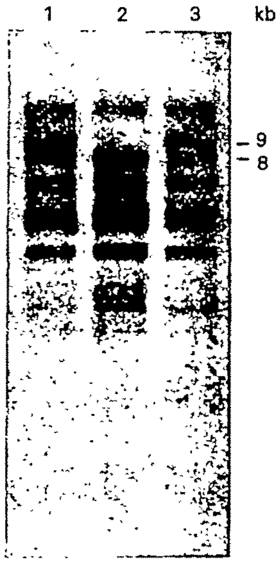


FIG. 2. Restriction fragment length polymorphism detected with probe p4.1, corresponding to locus *D19S7*. Lane 1: Mm heterozygote; lane 2: mm homozygote; lane 3: MM homozygote.

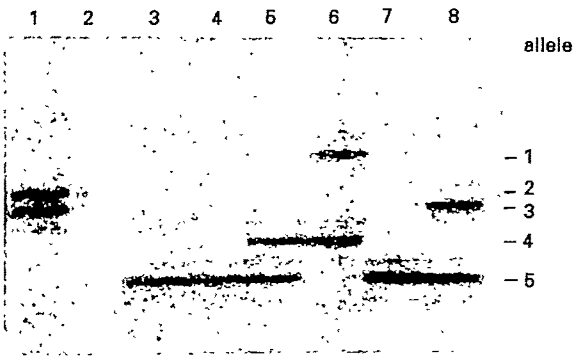


FIG. 3. Hypervariable microsatellite locus *D19S47* revealed using Mfd9 primers. Five bands of different sizes can be seen; any one individual possesses either one (homozygote) or two (heterozygote) of these marker alleles. Lane 1: 2,3 heterozygote; lane 2: no DNA (PCR control); lane 3: 5,5 homozygote; lane 4: 5,5 homozygote; lane 5: 4,5 heterozygote; lane 6: 1,4 heterozygote; lane 7: 5,5 homozygote; lane 8: 3,5 heterozygote.

polymorphisms (RFLP) [13] described in table I. The pattern observed on an autoradiograph showing an RFLP with the probe for D19S7 is shown in figure 2.

Hypervariable microsatellites

The human genome contains large numbers of very simple repeat sequences, such as the bases $(CA)_n$ where n may vary from 5 to about 20. Although their function (if any) is uncertain, they are found through many of the non-coding regions of chromosomes. The length of the repeat unit at any one chromosomal position usually varies from person to person (or chromosome to chromosome), so that typically five or more different lengths of these repeat sequences are present in the population. The consequence of this is that the length of the repeat unit is highly informative as a marker which may be used in the same way as RFLP for following the inheritance of individual chromosomes in family studies. For this reason, hypervariable microsatellite marker loci are being used increasingly in gene mapping and genetic diagnosis [14]. A marker of this type is visualized by amplifying the region containing the simple repeat from unique genomic sequences which have been identified as flanking it on each side, using the polymerase chain reaction. The length of the two repeat units found on the two chromosomes in each individual may then be determined by high resolution gel electrophoresis. Polymerase chain reactions to amplify the hypervariable regions were carried out essentially as described previously [15], except that radiolabelled ^{32}P-deoxycytidine triphosphate (dCTP) was used to label the DNA product. The primer sequences used specifically amplified the hypervariable microsatellite regions of Mfd5 and Mfd9, corresponding to the loci *APOC2* and *D19S47*, respectively. Both markers are known to be located on chromosome 19q [11]. The pattern of bands observed on an autoradiograph corresponding to alleles of the *D19S47* locus is illustrated in figure 3.

Linkage analysis

Linkage analysis was performed using the computer program LINKAGE v5.03 [16]. For the purpose of these linkage analyses, calculations have included the following assumptions in line with the recommendations of the genetics section of the European MH Group: a false negative rate on contracture testing of 2%; a false positive rate on contracture testing of 2%; frequency of the MH susceptibility allele 1 in 10000 in the population (corresponding to an incidence of 1 in 5000).

The LINKAGE program calculates the likelihood of obtaining the observed results with a specified degree of linkage, θ, between the susceptibility gene and the marker locus, compared with the likelihood of obtaining the same results in the absence of linkage. These likelihoods can be calculated for all degrees of recombination, θ, between 0.0 (complete linkage) and 0.5 (no linkage—that is, 50% recombination). By convention, relative likelihoods are expressed in the form of an odds ratio (for example, 10:1) against obtaining the observed linkage by chance. These likelihoods are then reported as logarithms ($\log_{10}$) of the likelihood, and are known as the "lod" (log **odds**) score. In this form, the likelihoods from different families can be combined

TABLE II. In vitro *contracture test results from members of families LMH3, LMH5 and LMH6, shown in figure 1. N = Normal; S = susceptible; E = equivocal. +ve = Patient determined as susceptible before the introduction of the full current European protocol. *Specimen not exposed to caffeine because of research projects. †Specimen taken for caffeine testing showed no evidence of viability*

	Halothane			Caffeine			
		Contracture strength (g)			Contracture strength (g)		
	Threshold (%)	At threshold	At 2%	Threshold (mmol/l)	At threshold	At 2 mmol litre^{-1}	Status
LMH3							
II-1	> 2			> 4			N
II-2	0.5	0.8	3.2	1.0	0.2	1.2	S
III-4	0.5	0.2	0.6	2.0	0.2	0.2	S
III-6	1.0	0.4	0.6	*	*	*	+ve
III-8	> 2			4.0			N
III-9	0.5	0.2	0.8	1.0	0.2	1.0	S
III-10	–	–	1.7	4.0			+ve
III-12	0.5	1.3	2.0	1.0	0.4	0.6	S
III-13	–	–	1.7	2.0	0.8	0.8	+ve
III-14	0.5	0.3	1.0	*	*	*	+ve
IV-2	> 2			4.0			N
IV-3	> 2			> 4			N
IV-5	–	–	1.8	> 4			+ve
IV-6	1.0	0.2	0.6	*	*	*	+ve
IV-7	> 2			> 4			N
IV-8	2.0	0.4	0.4	1.5	0.2	0.6	S
IV-9	> 2			4.0			N
LMH5							
I-1	> 2			> 4			N
II-2	0.5	1.0	2.2	> 4			+ve
II-4	1.0	1.4	2.0	*	*	*	+ve
III-2	> 2			> 4			N
III-3	1.0	1.0	1.2	0.25	1.1	4.6	S
III-4	1.0	0.4	1.4	*	*	*	+ve
III-5	> 2			> 4			N
LMH6							
II-1	> 2			> 4			N
II-2	0.5	1.3	1.3	3.0			E
II-4	1.0	0.5	1.0	1.0	0.3	1.1	S
II-5	> 2			3.0			N
III-4	0.5	0.5	1.8	0.5	0.2	0.5	S
III-5	> 2			4.0			N
III-8	0.5	1.0	1.6	1.0	0.3	0.8	S
III-10	0.5	0.2	0.8	–	–	–	E†
III-11	0.5	0.8	0.8	1.0	0.3	0.4	S
III-13	1.0	0.5	1.0	2.0	0.2	0.2	S
IV-1	> 2			3.0			N
IV-6	0.5	0.5	1.0	2.0	0.2	0.2	S

simply by adding the lod scores for each (equivalent to multiplying the likelihoods).

A lod score of +3 is generally regarded as sufficient to establish a putative linkage in the absence of previous data; however, a lod score of +2 (corresponding to odds of 100:1) may be regarded as confirming the linkage for subsequent families. A lod score of −2 or less is taken as evidence excluding genetic linkage over the region where it applies around the marker locus because recombination has been found between the disease gene and the marker. Lod scores calculated by the LINKAGE program can be tabulated for each pedigree and each marker for several values of the recombination fraction, θ, from 0.001 (0.1% recombination) up to 0.5.

RESULTS

Results of the *in vitro* contracture tests from members of families LMH3, LMH5 and LMH6 are shown in table II. The results of analysis of the linkage relationships between MH susceptibility and chromosome 19 markers are shown in the form of lod scores in table III. This statistical analysis provides evidence for a chromosome 19q location for the gene determining susceptibility to MH in some or all of these three families.

Close linkage is demonstrated between MH susceptibility and *D19S47*, the maximum lod score of +2.11 being found at a recombination fraction of 0.075. Significant linkage has not, however, been demonstrated in any individual family, possibly because the marker was not fully informative. The MH gene is located more distantly from *APOC2*, with a maximum lod score from all three families of +1.19 at a recombination fraction of 0.20. The region around *APOC2* itself is excluded in family LMH3 (lod score less than −2). Linkage to the region of the marker *D19S7*, which is located much nearer to the centromere of chromosome 19 and the other markers, is excluded for two of the families (LMH3 and LMH6).

TABLE III. *Linkage analysis for malignant hyperthermia and chromosome 19 markers. Lod scores are given for each family, and combined*

	Recombination fraction, θ							
	0.001	0.01	0.025	0.050	0.075	0.10	0.20	0.40
Interval: MH/D19S47 (Mfd 9)								
LMH 3	1.07	1.05	1.01	0.95	0.90	0.83	0.60	0.18
LMH 5	0.60	0.59	0.58	0.56	0.53	0.51	0.41	0.16
LMH 6	−0.95	0.02	0.37	0.59	0.68	0.72	0.65	0.15
Combined	0.72	1.66	1.96	2.10	2.11	2.06	1.66	0.49
Interval: MH/APOC2[CA]$_n$ (Mfd5)								
LMH 3	−7.45	−3.53	−2.02	−0.94	−0.37	−0.01	0.61	0.43
LMH 5	0.60	0.59	0.58	0.56	0.53	0.51	0.41	0.16
LMH 6	−1.57	−0.61	−0.31	−0.07	0.04	0.11	0.17	0.03
Combined	−8.42	−3.55	−1.75	−0.45	0.20	0.61	1.19	0.62
Interval: MH/D19S7 (p4.1)								
LMH 3	−2.12	−1.13	−0.74	−0.45	−0.29	−0.19	−0.01	0.01
LMH 5	−0.19	−0.19	−0.19	−0.17	−0.16	−0.15	−0.11	−0.03
LMH 6	−2.28	−1.29	−0.89	−0.61	−0.46	−0.36	−0.14	−0.02
Combined	−4.59	−2.61	−1.82	−1.23	−0.91	−0.70	−0.26	−0.04

DISCUSSION

Genetic linkage of the gene conferring susceptibility to malignant hyperthermia with the region of chromosome 19q close to the gene encoding the ryanodine receptor (*RYR1*) was first reported for Irish [7] and North American [17] families. The ryanodine receptor is a protein which contains a calcium release channel in the sarcoplasmic reticulum of skeletal muscle, so *RYR1* is attractive as a candidate gene for MH susceptibility. There is physiological evidence implicating an abnormality of the ryanodine receptor in both porcine [18] and human [19] MH susceptibility.

It is important to stress that the families in this present study were chosen because the typing of each individual as susceptible or non-susceptible was regarded as firm on the basis of the muscle contracture tests. The results presented here strongly suggest that the gene for MH susceptibility in one or more of these three British families is located in the same region of chromosome 19q. Whether or not *RYR1*, rather than another gene in the same region, is responsible for MH susceptibility in some or all of the families showing linkage to chromosome 19q is the subject of continuing work.

The question of genetic heterogeneity within MH susceptibility must also be examined. Families from North America and Central Europe have been reported which apparently exclude the relevant region of chromosome 19q from linkage with MH susceptibility [20, 21]. Indeed, it is possible that another region may be involved in one or two of the families reported here. Further studies on more families are needed to establish the proportions of families with MH susceptibility which map to chromosome 19 and to other regions of the genome. It also needs to be established if there is any correlation between the degree of sensitivity of the muscle of susceptible individuals to the *in vitro* contracture tests and linkage to chromosome 19. To facilitate progress in answering this question, we suggest that reports in this area include full contracture data, comprising the drug threshold for contracture, the strength of contracture at that threshold and the strength of contracture at 2% halothane (corresponding to 0.44 mmol litre^{-1}) and caffeine 2 mmol litre^{-1}, respectively.

In order to preserve international conformity, we have accepted the linkage analysis parameters for MH agreed by the genetics section of the European Malignant Hyperthermia Group. We think that these confidence limits are conservative when applied to our own data, and believe that this constitutes a suitable safeguard against drawing false conclusions.

Until the questions regarding the genetic heterogeneity of MH are resolved, it is clearly inappropriate to use the linkage of DNA marker loci as a diagnostic test for MH susceptibility in place of muscle contracture testing in a recognized centre.

ACKNOWLEDGEMENTS

We thank the following for financial support: Yorkshire Regional Health Authority (A.D.S., F.R.E. and J.L.H.); University of Oxford Medical Research Fund (H.R.D.).

REFERENCES

1. Ellis FR, Heffron JJA. Clinical and biochemical aspects of malignant hyperpyrexia. In: Atkinson RS, Adams AP, eds. *Recent Advances in Anaesthesia and Analgesia 15*. Edinburgh: Churchill Livingstone, 1985; 173–207.
2. Denborough MA, Forster JFA, Lovell RRH, Maplestone PA, Villiers JD. Anaesthetic deaths in a family. *British Journal of Anaesthesia* 1962; 34: 395–396.
3. Kalow W, Britt BA, Terreau ME, Haist C. Metabolic error of muscle metabolism after recovery from malignant hyperthermia. *Lancet* 1970; 2: 895–898.
4. Ellis FR, Harriman DGF, Keaney NP, Kyei-Mensah K, Tyrrell JH. Halothane induced muscle contracture as a cause of hyperpyrexia. *British Journal of Anaesthesia* 1971; 43: 721–722.
5. European Malignant Hyperpyrexia Group. A protocol for the investigation of malignant hyperpyrexia (MH) susceptibility. *British Journal of Anaesthesia* 1984; 56: 1267–1269.
6. Ellis FR, Halsall PJ, Harriman DGF. The work of the Leeds Malignant Hyperpyrexia Investigation Unit, 1971–84. *Anaesthesia* 1986; 41: 809–815.

7. McCarthy TV, Healy JMS, Heffron JJA, Lehane M, Deufel T, Lehmann-Horn F, Farrall M, Johnson K. Localisation of the malignant hyperthermia susceptibility locus to human chromosome 19q12-13.2. *Nature* (London) 1990; **343**: 562–564.
8. Hall LW, Woolfe N, Bradley JWP, Jolly DW. Unusual reaction to suxamethonium chloride. *British Medical Journal* 1966; **2**: 1305.
9. Archibald AL, Imlah P. The halothane sensitivity locus and its linkage relationship. *Animal Blood Groups and Biochemical Genetics* 1985; **16**: 253–263.
10. Fujii JK, Otsu K, Zorzato F, de Leon S, Knanna VK, Weiler J, O'Brien PJ, MacLennan DH. Identification of a mutation in the porcine ryanodine receptor that is associated with MH. *Science* 1991; **253**: 448–451.
11. Ropers HH, Pericak-Vance MA. Report of the committee on the genetic constitution of chromosome 19. *Human Gene Mapping 11: Cytogenetics and Cell Genetics* 1991; **58**: 751–784.
12. Old JM, Higgs DR. In: Weatherall DJ, ed. *Methods in Haematology 6*. Edinburgh: Churchill Livingstone, 1983; 74.
13. Weatherall DJ. *The New Genetics and Clinical Practice*, 3rd Edn. Oxford: Oxford University Press, 1991.
14. Weber JL, May PE. An abundant class of human DNA polymorphisms which can be typed using the polymerase chain reaction. *American Journal of Human Genetics* 1989; **44**: 388–396.
15. Taylor GR, Noble JS, Hall JL, Stewart AD, Mueller RF. Hypervariable microsatellite for genetic diagnosis. *Lancet* 1989; **2**: 454.
16. Lathrop GM, Lalouel JM. Easy calculations of lod scores and genetic risks on small computers. *American Journal of Human Genetics* 1984; **36**: 460–465.
17. MacLennan DH, Duff C, Zorzato F, Fujii J, Phillips M, Korneluk RG, Frodis W, Britt BA, Worton RG. Ryanodine receptor gene is a candidate for predisposition to malignant hyperthermia. *Nature (London)* 1990; **343**: 559–561.
18. Mickelson JR, Gallant EM, Litterer LA, Johnson KM, Rempel WE, Louis CF. Abnormal sarcoplasmic reticulum ryanodine receptor in malignant hyperthermia. *Journal of Biological Chemistry* 1988; **263**: 9310–9315.
19. Hopkins PM, Ellis FR, Halsall PJ. Ryanodine contracture: A potentially specific *in vitro* diagnostic test for malignant hyperthermia. *British Journal of Anaesthesia* 1991; **66**: 611–613.
20. Levitt RC, Nouri N, Jedlicka AE, McKusick VA, Marks AR, Shutack JG, Fletcher JE, Rosenberg H, Meyers DA. Evidence for genetic heterogeneity in malignant hyperthermia susceptibility. *Genomics* 1991; **11**: 543–547.
21. Deufel T, Meitinger T, Golla A, Johnson K, MacLennan DH, Lehmann-Horn F. Two recombinations between malignant hyperthermia susceptibility and human ryanodine receptor in a single family: another gene for MHS? *Human Gene Mapping 11: Cytogenetics and Cell Genetics* 1991; **58**: 2018–2019.

British Journal of Anaesthesia 1993; 70: 76–79

IN VITRO EFFECT OF EPHEDRINE, ADRENALINE, NORADRENALINE AND ISOPRENALINE ON HALOTHANE-INDUCED CONTRACTURES IN SKELETAL MUSCLE FROM PATIENTS POTENTIALLY SUSCEPTIBLE TO MALIGNANT HYPERTHERMIA

A. URWYLER, K. CENSIER, M. D. SEEBERGER, J. M. ROTHENBÜHLER, M. A. KAUFMANN AND J. DREWE

SUMMARY

We have measured the effects of ephedrine, adrenaline, noradrenaline and isoprenaline on halothane-induced contractures in muscle biopsies from patients potentially susceptible to malignant hyperthermia (MH). At concentrations of 4–24 mmol litre^{-1}*, ephedrine induced* in vitro *contractures in halothane 0.44 mmol litre*$^{-1}$*-prechallenged muscle, whilst adrenaline, noradrenaline and isoprenaline had no effect. There was a shift of the ephedrine concentration–response curve to the left and an increased maximum muscle contracture in the MH susceptible group compared with the MH negative group (*$P < 0.001$*). We conclude that ephedrine increased halothane-induced muscle contractures* in vitro *either by an unknown pharmacological mechanism or by an adrenergic stimulation which was different from those of the other investigated adrenoceptor agonists.* (Br. J. Anaesth. 1993; **70**: 76–79)

KEY WORDS

Hyperthermia: malignant. Muscle: halothane-induced contracture. Sympathetic nervous system, pharmacology: adrenaline, ephedrine, isoprenaline.

Malignant hyperthermia (MH) is characterized clinically by a life-threatening hypermetabolic reaction that is attributed to an underlying muscle disease. Skeletal muscle from MH susceptible (MHS) individuals demonstrates abnormal *in vitro* contractures to halothane, in contrast with muscle bundles from MH negative (MHN) subjects [1, 2]. *In vitro* muscle contractures are characterized by an increase in baseline tension and are related to an increased myoplasmic calcium concentration $[Ca^{2+}]_i$ [3]. There is controversy as to whether or not the sympathetic system is involved primarily or as a secondary response to MH [4], and less is known about the effects of adrenergic agents on muscle metabolism in humans with an acute MH episode. Therefore, we have investigated the effects of different adrenoceptor agonists on halothane-induced muscle contractures *in vitro* in patients potentially susceptible to MH. Some of these results have been published previously in abstract form [5].

PATIENTS AND METHODS

We studied 42 potentially MHS individuals after approval by the University of Basel's Hospital Ethics Committee. All patients gave informed written consent. Biopsies were taken from the vastus medialis muscle under regional anaesthesia with a femoral nerve block using 1.5% mepivacaine 5–7.5 mg kg^{-1}. The muscle tissue was maintained in Krebs–Ringer solution oxygenated with 5% carbon dioxide in oxygen (carbogen) until the experiments were performed. Muscle bundles, approximately 2.5 cm long and 2–3 mm in diameter, were mounted in a test bath containing Krebs–Ringer solution. Temperature was maintained at 37 °C and the bath was bubbled continuously with carbogen. Supramaximal electrical stimulation at 0.2 Hz was used to demonstrate the viability of the muscle bundle. MH susceptibility was evaluated with two halothane and two caffeine tests on four different muscle bundles, and MH diagnosis was made according to a standardized procedure [2, 6].

Surplus muscle bundles were challenged for 10 min with halothane 0.44 mmol litre^{-1} in the test bath, corresponding to 2% in the gas phase, followed by incremental doses of adrenaline ($n = 3$), noradrenaline ($n = 6$), isoprenaline ($n = 3$) or ephedrine ($n = 42$). Twelve bundles were pretreated with incremental doses of ephedrine 4–24 mmol litre^{-1} before the halothane 0.44 mmol litre^{-1} challenge. All drugs were dissolved in Krebs–Ringer solution (pH 7.4) before addition to the test bath. In preliminary experiments, concentrations between 1 nmol litre^{-1} and 1 mmol litre^{-1} of all adrenergic agents studied

---

A. URWYLER, M.D., K. CENSIER, M. D. SEEBERGER, M.D., M. A. KAUFMANN, M.D., J. DREWE, M.D. (Department of Anaesthesia and Research); J. M. ROTHENBÜHLER, M.D. (Department of Surgery); University of Basel, Kantonsspital, CH-4031 Basel, Switzerland.
Accepted for Publication: July 7, 1992.

did not initiate any muscle contractures [unpublished results], and thus each adrenoceptor agonist was evaluated at greater concentrations: 4, 8, 12, 16 and 24 mmol litre^{-1}. Drug concentrations were maintained for at least 3 min or until a steady state in baseline tension was achieved. Muscle contractures were recorded for each concentration of the various agents. The baseline value just before addition of the first dose of an adrenergic agonist was used as the zero level.

Drugs were obtained from the following commercial sources: halothane from Halocarbon Laboratories, Hackensack, NJ, U.S.A.; pure caffeine from Merck, Darmstadt, Germany; (−)-adrenaline hydrochloride (HCl), (−)-noradrenaline HCl, (−)-isoprenaline HCl, (−)-ephedrine HCl from Sigma Chemical Co., St Louis, MO, U.S.A.

Data analysis

Ephedrine concentration–response curves were calculated by non-linear regression analysis according to the sigmoidal maximum effect model (Hill equation) (SAS, Release 6.03, U.S.A.). Data are presented as mean (SEM) and 95% confidence intervals (95% CI). Statistical analyses were performed using multiple one-sided or two-sided Student's t tests with Bonferroni correction as appropriate. $P < 0.05$ was considered to represent a significant difference between the groups.

RESULTS

Sixteen individuals were classified as MHN, while 26 patients were considered to be clinically MHS (fig. 1). The clinically MHS group consisted of 17 individuals who had abnormal contracture tests to halothane and caffeine challenges and a second group of nine MH equivocal patients (MHEh) with abnormal halothane but normal caffeine contracture tests.

In muscle bundles from 12 patients (MHN: $n = 5$; MHS: $n = 7$), administration of ephedrine before halothane did not produce any contractures. However, when halothane was added to the test bath after pretreatment with ephedrine, all muscle bundles demonstrated contractures (12.6 (3.6) mN (95% CI 2.6–22.6 mN) in the MHN group compared with 43.9 (10.3) mN (95% CI 18.6–69.1 mN) in the MHS group).

After the halothane 0.44 mmol litre^{-1} challenge, there were no muscle contractures in bundles of MHS individuals after addition of adrenaline, noradrenaline or isoprenaline to the test bath, whilst ephedrine induced dose-dependent muscle contractures in all these muscle bundles (table I, fig. 2).

There was a significant shift of the ephedrine concentration–response curve to the left for the MHS group compared with the MHEh and MHN groups (table II, fig. 3). Eight patients had to be excluded for the calculations of EC$_{50}$ and the maximum effect (*E*max), because there were no muscle contractures in response to ephedrine ($n = 4$ in the MHN group) or because *E*max was not achieved in the range of the investigated concentra-

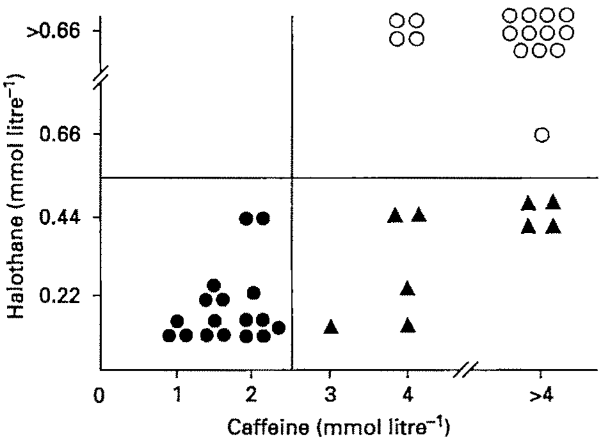


FIG. 1. Classification of 42 patients investigated with *in vitro* muscle contracture tests according to the procedure of the European Malignant Hyperpyrexia Group [2]. For the diagnosis of MH susceptibility the threshold concentrations of halothane and caffeine were used which initiated an *in vitro* muscle contracture ≥ 2 mN. MHN (○) ($n = 16$) = MH negative; MHS (●) ($n = 17$) = MH susceptible (abnormal halothane and abnormal caffeine contracture tests); MHEh (▲) ($n = 9$) = MH equivocal (abnormal halothane but normal caffeine contracture tests).

TABLE I. In vitro *contractures (≥ 2 mN) initiated by various adrenoceptor agonists in 29 muscle bundles from MHS subjects. Each adrenoceptor agonist was evaluated at increasing concentrations (4, 8, 12, 16 and 24 mmol litre^{-1}) in the presence of halothane 0.44 mmol litre^{-1}*

	Number of contractures	Number tested
(−)-Ephedrine	17	17
(−)-Adrenaline	0	3
(−)-Noradrenaline	0	6
(−)-Isoprenaline	0	3
(−)-Ephedrine after (−)-adrenaline	3	3
(−)-Ephedrine after (−)-noradrenaline	6	6
(−)-Ephedrine after (−)-isoprenaline	3	3

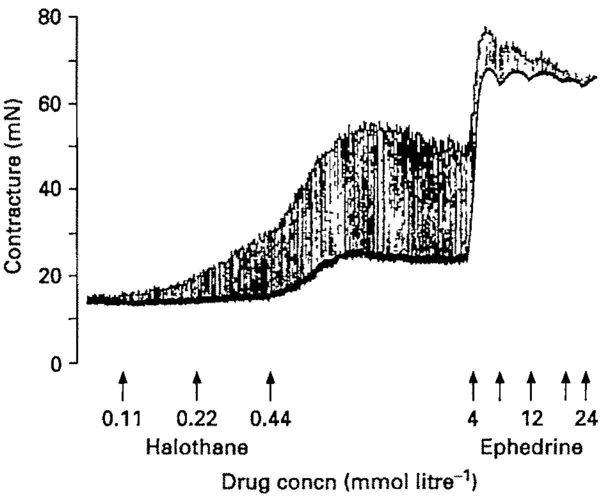


FIG. 2. Representative curve of halothane and ephedrine effects on the *in vitro* muscle contracture of an MHS individual. Contractions were elicited using supramaximal electrical stimulation (0.2 Hz) to prove the viability of the muscle bundle. Halothane and ephedrine were added to the test bath in increasing concentrations as indicated (labels 8 and 16 (mmol litre^{-1}) omitted for ephedrine, for clarity.)

TABLE II. In vitro *effect of ephedrine on halothane-induced muscle contractures (mean (SEM) [95% confidence intervals]). Significant changes (multiple one-sided* t *test with Bonferroni correction):* *P < *0.05 (compared with MHN group);* †P < *0.05 (compared with MHEh group);* ***P < *0.001 (compared with MHN group)*

	n	*E*max (mN)	EC_{50} (mmol litre^{-1})
MHN	12	17 (3.2) [10–24]	11.8 (1.1) [9.3–14]
MHEh	7	20 (3.9) [11–30]	9.4 (1.9) [4.8–14]
MHS	15	29 (4)* [20–38]	4.6 (1)†*** [2.5–6.8]

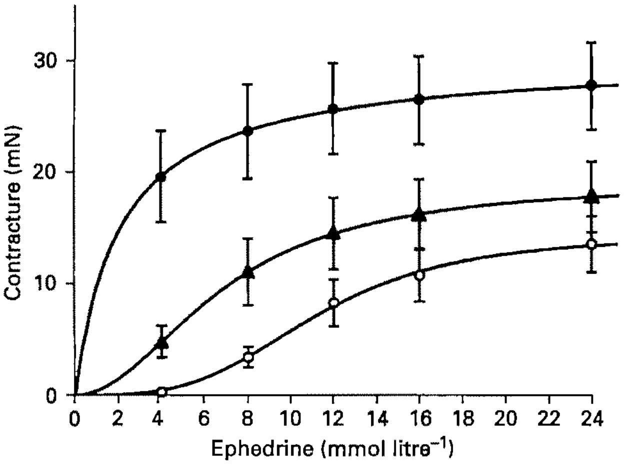


FIG. 3. Mean (SEM) *in vitro* effect of ephedrine on halothane-induced contractures in muscle bundles from patients potentially susceptible to malignant hyperthermia. MHS (●) ($n = 17$) = MH susceptible (abnormal halothane and caffeine contracture); MHEh (▲) ($n = 9$) = MH equivocal (abnormal halothane but normal caffeine contracture); MHN (○) ($n = 16$) = MH negative.

tions ($n = 1$ in the MHN group, $n = 2$ in the MHEh group and $n = 1$ in the MHS group).

DISCUSSION

In this study, ephedrine 4–24 mmol litre^{-1} increased halothane-induced *in vitro* muscle contractures, whilst adrenaline, noradrenaline and isoprenaline had no effect. There was a statistically significant shift of the ephedrine concentration–response curve to the left in the MHS group compared with the MHN group. These data suggest the possibility that ephedrine increased muscle metabolism *in vitro*. However, the exact mechanism of the *in vitro* effect of ephedrine on skeletal muscle is speculative.

In general, ephedrine is considered to have direct and indirect sympathomimetic effects, but the exact pharmacological mechanism(s) is not known [7]. Because inositol 1,4,5-triphosphate (IP_3) has been found to be increased in muscle tissue from MHS pigs and MHS humans [8, 9], one could speculate that ephedrine might increase intracellular IP_3 concentrations and thereby increase halothane-induced muscle contractures. Alternatively, or in addition to IP_3, it may be that ephedrine effects are mediated indirectly by cyclic AMP, comparable to the effects of theophylline or caffeine on skeletal muscle *in vitro* [10]. Recent work has shown the possible involvement of a mutation of the ryanodine receptor gene as the primary defect in MHS individuals [11, 12]. Therefore, it may be interesting to determine if ephedrine interacts directly or indirectly with the ryanodine receptor.

If ephedrine initiates muscle contractures by an adrenergic effect, this mechanism must differ from classical adrenergic stimulation because adrenaline, noradrenaline and isoprenaline did not have similar effects. Little is known about the adrenergic effects on halothane-induced *in vitro* muscle contractures. To our knowledge, only noradrenaline in porcine skeletal muscle [13] and salbutamol, a $beta_2$-adrenoceptor agonist, in human skeletal muscle have been investigated [14]. Both adrenoceptor agonists did not potentiate halothane-induced muscle contractures. Our study provides additional evidence that the sympathomimetic system does not initiate MH primarily [15, 16], as we did not find any contractures in muscle bundles from MHS individuals after challenges with adrenaline or noradrenaline.

The clinical relevance of *in vitro* muscle investigations, as performed in the present study, is unclear, as we used ephedrine in concentrations of 4–24 mmol litre^{-1}, 1000–2000-fold greater than clinically relevant plasma concentrations. However, these large concentrations of ephedrine *in vitro* could reflect the requirement that effective tissue concentrations can be achieved by diffusion, in contrast to the situation *in vivo* when ephedrine is brought into muscle tissue by capillary circulation. Clinically, ephedrine increases energy expenditure [17, 18] and has been proposed as a thermogenic drug for the treatment of obesity [19] and cyclical hypothermia [20] or for the improvement of cold tolerance [21]. Leg oxygen consumption increased 60% after ephedrine administration and it was speculated that 50% of the increase in oxygen consumption induced by ephedrine may take place in skeletal muscle [17]. In anaesthetics, ephedrine is used for vasopressor therapy in hypotension as a result of regional or general anaesthesia [21]. To our knowledge, there are no clinical data suggesting ephedrine as a MH trigger. However, these data suggest the use of alternative adrenergic drugs if cardiovascular instability is associated with a hypermetabolic state in MHS individuals.

REFERENCES

1. Ellis FR, Harriman DGF, Keaney NP, Kyei-Mensah K, Tyrrell JH. Halothane-induced muscle contracture as a cause of hyperpyrexia. *British Journal of Anaesthesia* 1971; **43**: 721–722.
2. European Malignant Hyperpyrexia Group. A protocol for the investigation of malignant hyperpyrexia (MH) susceptibility. *British Journal of Anaesthesia* 1984; **56**: 1267–1269.
3. Iaizzo PA, Klein W, Lehmann-Horn F. Fura-2 detected myoplasmic calcium and its correlation with contracture force in skeletal muscle from normal and malignant hyperthermia susceptible pigs. *Pflügers Archiv* 1988; **411**: 648–653.
4. Gronert GA, Mott J, Lee J. Aetiology of malignant hyperthermia. *British Journal of Anaesthesia* 1988; **60**: 253–267.
5. Urwyler A, Censier K, Rothenbühler JM. *In vitro* effect of ephedrine in malignant hyperthermia susceptible muscle. *Journal of the Neurological Sciences* 1990; **98** (Suppl.): 520.
6. Urwyler A, Funk B, Censier K, Drewe J. Effect of halothane equilibration kinetics on *in vitro* muscle contractures for

malignant hyperthermia screening. *Acta Anaesthesiologica Scandinavica* 1992; **36**: 115–118.

7. Hoffman BB, Lefkowitz RJ. Catecholamines and sympathomimetic drugs. In: Gilman A, Rall TW, Nies AS, Taylor P, eds. *Goodman and Gilman's The Pharmacological Basis of Therapeutics*. New York: Pergamon Press, 1990; 187–220.
8. Foster PS, Gesini E, Claudianos C, Hopkinson KC, Denborough MA. Inositol 1,4,5-triphosphate phosphatase deficiency and malignant hyperpyrexia in swine. *Lancet* 1989; 2: 124–127.
9. Scholz J, Troll U, Schulte am Esch J, Hartung E, Patten M, Sandig P, Schmitz W. Inositol-1,4,5-triphosphate and malignant hyperthermia. *Lancet* 1991; **337**: 1361.
10. Flewellen EH, Nelson TE. Is theophylline, aminophylline, or caffeine (methylxanthines) contraindicated in malignant hyperthermia susceptible patients? *Anesthesia and Analgesia* 1983; **62**: 115–118.
11. MacLennon DH, Duff C, Zorzato F, Fujii J, Phillips M, Korneluk RG, Frodis W, Britt BA, Worton RG. Ryanodine receptor gene is a candidate for predisposition to malignant hyperthermia. *Nature (London)* 1990; **343**: 559–561.
12. McCarthy TV, Healy JMS, Heffron JA, Lehane M, Deufel T, Lehmann-Horn F, Farrall M, Johnson K. Localization of the malignant hyperthermia susceptibility locus to human chromosome 19q12-13.2. *Nature (London)* 1990; **343**: 562–564.
13. Sim ATR, White MD, Denborough MA. Effects of adenylate cyclase activators on porcine skeletal muscle in malignant hyperpyrexia. *British Journal of Anaesthesia* 1987; **59**: 1557–1562.
14. Bendixen D, Ording H. Influence of salbutamol on the in vitro muscle response to caffeine and halothane in malignant hyperthermia. *Acta Anaesthesiologica Scandinavica* 1990; **34**: 658–661.
15. Gronert GA, White DA. Failure of norepinephrine to initiate porcine malignant hyperthermia. *Pflügers Archiv* 1988; **411**: 226–228.
16. Haeggendal J, Joensen L, Carlsten J. The role of sympathetic activity in initiating malignant hyperthermia. *Acta Anaesthesiologica Scandinavica* 1990; **34**: 677–683.
17. Astrup A, Buelow J, Madasen J, Christensen NJ. Contribution of BAT and skeletal muscle to thermogenesis induced by ephedrine in man. *American Journal of Physiology* 1985; **248**: E507–E515.
18. Vallerand AL, Jacobs I, Kavanagh MF. Mechanism of enhanced cold tolerance by an ephedrine–caffeine mixture in humans. *Journal of Applied Physiology* 1989; **67**: 438–444.
19. Dulloo AG, Miller DS. Prevention of genetic fa/fa obesity with an ephedrine–methylxanthines thermogenic mixture. *American Journal of Physiology* 1987; **252**: R507–R513.
20. Flynn MD, Sandeman DD, Mawson DM, Shore AC, Tooke JE. Cyclical hypothermia: successful treatment with ephedrine. *Journal of the Royal Society of Medicine* 1991; **84**: 752.
21. Ramanthan S, Grant GJ. Vasopressor therapy for hypotension due to epidural anesthesia for Caesarean section. *Acta Anaesthesiologica Scandinavica* 1988; **32**: 559–565.

British Journal of Anaesthesia 1993; **70**: 80–86

REVIEW ARTICLE

THE ROLE OF RECOMBINANT GROWTH FACTORS IN TRANSFUSION MEDICINE

L. T. GOODNOUGH

There is renewed interest in alternatives to blood transfusion. The changing environment of transfusion medicine includes increased awareness of patients and physicians as to the problems of safety of blood, desirability of blood conservation, and informed consent before elective blood transfusion [29]. For example, physicians may be more conservative in respect of the PCV at which transfusion is indicated [14] in anaemic medical and surgical patients [56]. This includes orthopaedic surgery patients who choose to predeposit autologous blood [55]. Similarly, the use of blood and blood components has been reduced substantially by the use of strategies for blood conservation during surgery. A combination of techniques such as preoperative autologous blood donation, acute haemodilution, use of non-blood pump prime, intra- and postoperative autologous blood salvage and reinfusion and, most importantly, acceptance of normovolaemic anaemia after operation, have resulted in a reduction in red blood cell transfusion in the United States [52].

In addition to these methods of blood conservation, recombinant growth factors now show promise in reducing or eliminating the requirement for homologous blood components, when used in combination with other blood conservation methods in a variety of clinical circumstances. This review considers recent developments in this area, including the haematopoietic growth factor recombinant human erythropoietin (rHuEPO), and the myeloid growth factors granulocyte colony stimulating factor (G-CSF) and granulocyte–macrophage colony stimulating factor (GM-CSF).

STIMULATION OF HAEMATOPOIESIS: ERYTHROPOIETIN

The development of rHuEPO, from identification as the hormone regulating erythropoiesis [7], to purification and identification [41] of human urinary erythropoietin, and subsequent cloning, expression and characterization as a recombinant product [6, 36, 53], has occurred in the relatively brief period of only 32 years (1953–1985). Furthermore, the extension of this advance to direct use in the clinical treatment of anaemias has occurred within the very short interval of only 2 years.

Erythropoietin is a circulating plasma polypeptide comprising 166 amino acids; it is heavily glycosylated, with a molecular weight of approximately 34000. Purified rHuEPO has an amino acid sequence identical to that of human urinary erythropoietin [41]. The natural and urinary hormones are indistinguishable from rHuEPO on the basis of all immunological and biological comparisons performed to date, the carbohydrate composition and both immunological and biological properties. rHuEPO is more than 98% pure, with a specific activity of more than 100000 u/mg of hormone [6]. To date, there has not been a report of a patient who has developed alloantibodies to rHuEPO. From its initial use in patients with anaemia caused by renal failure, the potential uses of rHuEPO have expanded to many areas of surgical and medical anaemias.

Erythropoietin therapy in elective surgery

In elective surgery, preoperative autologous blood donation represents an attractive alternative to homologous blood transfusion. Potential candidates for autologous blood donation before surgery include any patient undergoing a procedure for which blood type and crossmatch was requested. The underutilization of autologous donation before elective surgery, demonstrated previously [53], can be improved with a co-ordinated programme involving hospital blood bank, information services and clinicians [35]. Nonetheless, a previous study has shown that orthopaedic patients predeposit insufficient autologous blood to obviate subsequent exposure to homologous blood [31]. At the University Hospitals of Cleveland, we have audited the homologous blood transfusion needs in elective orthopaedic surgical patients who did not become autologous blood donors and have shown that a significant percentage of patients require substantial amounts of blood transfusion (table I) [24]. For example, 45% of elective hip replacements and 15% of elective knee operations required administration of ⩾4 u of homologous blood. Potential problems limiting the procurement of autologous blood sufficient to meet these significant blood transfusion needs before orthopaedic surgery include: underordering by surgical staff; limitations of the storage interval; erythropoietic response to phlebotomy.

(Br. J. Anaesth. 1993; **70**: 80–86)

KEY WORDS
Blood: erythrocytes, haemopoietin. Transfusion.

LAWRENCE TIM GOODNOUGH, M.D., Department of Medicine, University Hospitals of Cleveland, 2074 Abington Road, Cleveland, Ohio 44106, U.S.A.

TABLE I. *Number (%) of patients without autologous blood predonation who subsequently received homologous blood transfusion in elective orthopaedic surgery. (From reference [24], with permission)*

Procedure	Blood transfused (u)							
	0	1	2	3	4	5	6	≥ 7
Hip ($n = 275$)	19 (6.9)	18 (6.5)	67 (24)	48 (18)	60 (22)	25 (9.1)	16 (5.8)	22 (8.0)
Knee ($n = 223$)	62 (28)	16 (7.2)	78 (35)	35 (16)	12 (5.4)	10 (4.5)	3 (1.3)	7 (3.1)
Spine ($n = 450$)	289 (64)	26 (5.7)	58 (13)	29 (6.4)	25 (5.5)	5 (1.1)	10 (2.2)	8 (1.8)
Misc. ($n = 279$)	214 (77)	4 (1.4)	25 (9)	10 (3.6)	11 (3.9)	6 (2.2)	3 (1.1)	6 (2.2)

A continuing medical education (CME) programme can correct the problem of underordering. Subsequent exposure to homologous blood in patients who successfully stored the amount of autologous blood requested by orthopaedic surgeons was reduced to 19 (13 %) of 145 patients in one study [31]. CME had no impact, however, on the effective storage interval (the time interval from day of surgical scheduling until date of surgery) during which blood can be collected for elective surgery. The mean storage interval before and after a CME programme has been shown to remain at 21 days [32], despite the ability to procure and store liquid blood up to a maximum of 42 days before transfusion. Exposure to homologous blood has been demonstrated to be unrelated to surgical underordering of autologous blood. Of 58 patients who were asked to donate ≥ 4 u, 23 (40 %) were deferred and nine of 23 (39 %) subsequently received homologous blood, compared with only seven of 117 (6 %) patients deferred when asked to donate ≤ 3 u; but four of these seven (57 %) subsequently received homologous blood. It has thus been demonstrated that when an autologous donation programme is accompanied by a CME programme, exposure to homologous blood is related to the donor deferral rate, rather than surgical underordering or inappropriate transfusion.

In the studies described above, the erythropoietin response to mild anaemia (PCV ≥ 33 %) was inadequate to allow autologous donation of the requested number of units in 30 of 175 patients and in 23 of 58 patients asked to store ≥ 4 u. Thus erythropoietic response to phlebotomy is the third limiting factor in the procurement of autologous blood sufficient to minimize the need for subsequent exposure to homologous blood. The American Association of Blood Banks has guidelines for elective, preoperative, autologous blood donation that include a haemoglobin concentration of not less than 11 g dl^{-1} or a PCV of not less than 33 %, and phlebotomy no more frequent than every 3 days and not within 72 h of surgery [50]. Previous studies on the relationship between decreasing packed red blood cell volume and endogenous immunoreactive plasma erythropoietin have indicated that this relationship is linear at haemoglobin concentrations less than approximately 11.5 g dl^{-1} [10]; at greater values there is no linear relationship, indicating that significant losses of red cell volume are required to stimulate endogenous erythropoietin. Studies have confirmed that the mild, iatrogenic anaemia induced by serial phlebotomy in autologous blood donors is not accompanied by an endogenous erythropoietin response adequate to stimulate compensatory bone marrow erythropoiesis [21, 34]. An analysis of autologous blood showed a linear decrease in mean red cell volume (donor PCV % multiplied by blood volume donated) with sequential donations, demonstrating an absence of compensatory erythropoiesis under normal blood donation conditions (fig. 1) [20]. When the red cell volumes of autologous blood were compared with male and female homologous blood, 20 % of autologous blood had red cell volumes less than the lower 95 % confidence interval for homologous blood units [20]. Thus not only do autologous blood donors have difficulty in predonating the amount of blood requested for surgery, but the oxygen-carrying capacity of sequential units of autologous blood donated is significantly less than that of homologous blood.

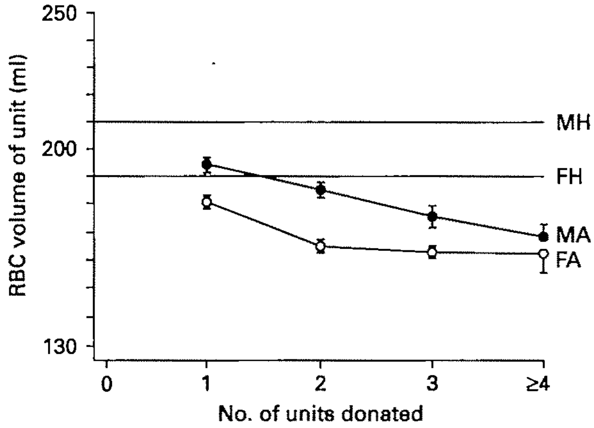


FIG. 1. Mean red blood cell (RBC) mass of blood units donated by 300 homologous donors compared with 79 autologous donors. Red cell mass was determined by multiplying blood volume donated times donation PCV (%). M = Male; F = female; H = homologous; A = autologous. (From reference [20], with permission).

The effectiveness of autologous blood donation in conserving homologous blood donation has been demonstrated for both open heart surgery [42] and orthopaedic surgery [28]. Figure 2 illustrates the extent of homologous blood transfusion in orthopaedic surgery, both for patients who were autologous blood donors and for non-autologous patients [27]. The likelihood of homologous blood transfusion declined for both groups over a 3-year interval, suggesting an increase in the threshold for transfusion; during this period, the mean number of autologous blood units donated by patients did not change, and there were no additional conservation techniques such as intra- or postoperative autologous blood salvage. Table II illustrates the homologous

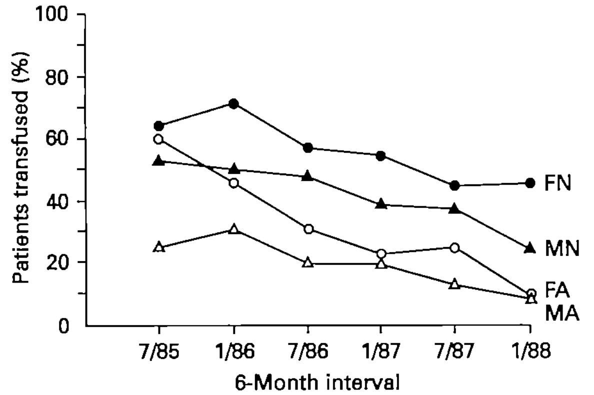


FIG. 2. Percentage of patients receiving homologous blood transfusion in autologous (A) compared with nonautologous (N) groups. The percentage of patients transfused with homologous blood declined from 60% for male (M) and 43% for female (F) nonautologous blood patients and from 35% (M) and 60% (F) in autologous donors in the first 6-month interval to 17% (all groups) in the last 6 months. (From reference [27], with permission.)

TABLE II. *Number of patients who had predonated autologous blood at the University Hospitals of Cleveland in the period July 1, 1985–June 30, 1988 and subsequently received homologous blood transfusion in elective orthopaedic surgery. (From reference [18], with permission)*

	Blood transfused (u)						
Procedure	1	2	3	4	5	6	Total
Hip ($n = 152$)	0	1	5	9	11	4	30
Knee ($n = 89$)	0	1	1	6	3	3	14
Spine ($n = 150$)	0	0	4	7	7	6	24
Misc. ($n = 39$)	0	1	0	2	1	0	4
Total ($n = 430$)	0	3	10	24	22	13	72 (16.7%)

blood needs of autologous blood donors in hip, knee and spinal surgery [18]. No patient received only 1 u of homologous blood, again demonstrating a conservative approach by the physician. However, several patients required 3–6 u of homologous blood in addition to the autologous blood units donated. A significant, preoperative, increased production of red cell volume would be necessary in order to generate the volume of autologous blood equivalent to the subsequent requirement for homologous blood in these patients.

These results suggested that treatment with rHuEPO would prevent the development of anaemia in these patients and increase the volume of autologous blood that could be collected before surgery. This was confirmed in a randomized, double-blind, placebo-controlled, multicentre study to determine if erythropoietin therapy could facilitate preoperative autologous blood donation [26]. Patients receiving erythropoietin 600 μg kg^{-1} i.v. twice weekly donated a 41% greater red blood cell volume compared with placebo-treated patients (fig. 3). Analysis of changes in PCV in these patients suggested that the equivalent of approximately 4 u of blood could be generated by this method [19] thus providing a rationale for the elimination of homologous blood transfusion.

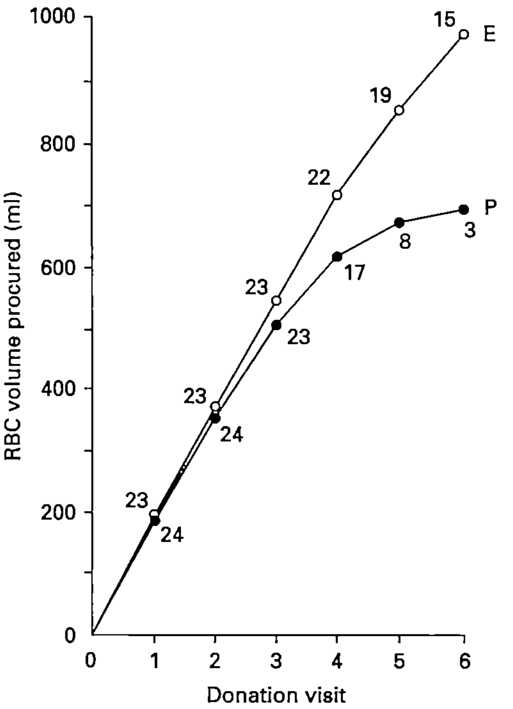


FIG. 3. Cumulative red blood cell (RBC) volume procured per patient. Number of patients at each donation is indicated. Mean cumulative interval (days) for each visit: visit 2 = 3.5; visit 3 = 7.2; visit 4 = 10.6; visit 5 = 14.2; visit 6 = 17.6. E = Erythropoietin; P = placebo. (From reference [26], with permission.)

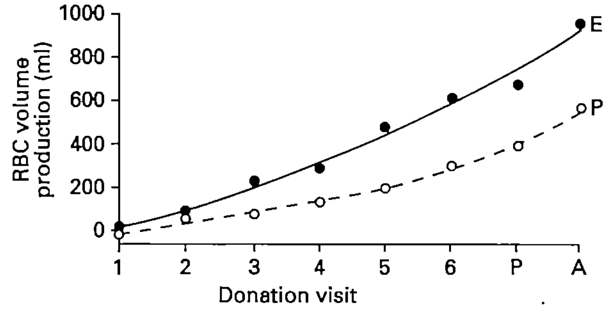


FIG. 4. Red blood cell (RBC) volume before operation during autologous blood donation, in 24 placebo- (○) and 23 erythropoietin- (●) treated patients. Data points represent calculated total volume of RBC (both *in vivo* and *ex vivo*) at donation visits 1–6, post-study visit (P) and at admission to hospital (A). The time required to expand RBC by 200 ml (equivalent to homologous blood 1 u [26]) can be derived for any preoperative interval. E = Erythropoietin; P = placebo.

Further analysis of preoperative red blood cell production (taking into account both *in vivo* and *ex vivo* (stored) red blood cell volumes) indicated that patients who underwent aggressive autologous blood phlebotomy did have a significant (27%) preoperative expansion of red blood cell volume (fig. 4), together with accelerated erythropoiesis at the time of surgery [25]. However, the increase (47%) observed in patients treated with erythropoietin was significantly greater. The major difference in red blood cell production between the placebo and erythropoietin groups occurred early in the collection period; by the time of surgery, there may have been an endogenous erythropoietin effect in the placebo patients sufficient to have diminished the differences between groups [33]. This result was undoubtedly dependent on the attempted removal of blood at the rate of 2 u per week, but not all patients can tolerate such a schedule [4]. For some, such as patients undergoing coronary artery bypass graft surgery, the limiting factor may be the loss of oxygen-carrying capacity, with a PCV of about 30 % [23]. As the increased erythropoiesis may be attributed to the drug rather than to frequent phlebotomy in erythropoietin-treated patients, more modest autologous blood procurement, coupled with administration of erythropoietin, may be preferable [4, 24] in patients unsuited for frequent autologous phlebotomy. Our analysis of preoperative red blood cell production in erythropoietin-treated patients indicates that the autologous blood equivalent of nearly 5 u of homologous blood may be generated by this method [25]. Clinical trials to demonstrate this are in progress in elective orthopaedic and elective coronary artery bypass surgery [19].

This analysis indicates that, for surgical procedures associated with significant blood loss requiring large transfusion needs (e.g. blood $\geqslant$ 4 u), an active programme of procurement of autologous blood is necessary in order to minimize exposure to homologous blood. The value of erythropoietin would be not only to facilitate procurement of autologous blood, but also to prevent the anaemia associated with blood donation in individuals who may have medical risks and poor tolerance for anaemia, frequent phlebotomy, or both [4, 24, 25, 33].

Prudent use of erythropoietin suggests that this agent should be administered in relation to actual blood losses arising from either autologous blood donation or surgical bleeding, in order to avoid the potential complications of polycythaemia and increased blood viscosity [44]. Its use to correct preoperative anaemia should, ideally, be coupled with procurement of autologous blood when the PCV exceeds 33 % [50], not only for these safety concerns, but also to enhance the effectiveness of this therapy in reducing homologous blood transfusion; most blood transfusion in coronary artery bypass surgery, for example, is given on the day of operation and this could be avoided if autologous blood were available before operation [30]. Clinical trials which use exposure to homologous blood as an outcome indicator are currently in progress. Finally, the optimal dose, route and interval of administration for erythropoietin therapy have yet to be established and are the object of current studies [22], the results of which may fulfil the promise of erythropoietin as a new tool in blood conservation as an alternative to homologous blood transfusion in elective surgery [29].

Non-elective surgery

Recombinant erythropoietin also has potential application in patients undergoing non-elective surgical procedures. rHuEPO has been shown to elicit a reticulocyte response within 2.7–3.5 days of administration and a PCV response within 7 days during blood loss in humans [26] and after blood loss in animals [37]. A recent report demonstrated the benefit of rHuEPO therapy in Jehovah's Witnesses undergoing cardiac surgery [16]. Thus pharmacological approaches to blood conservation in the perioperative setting may be expected to have important effects in reducing exposure to homologous blood. A clinical study is in progress to determine the efficacy of perisurgical rHuEPO in open heart surgery [22].

Renal insufficiency

For anaemias related to medical illness, rHuEPO therapy has been shown to be effective and is currently approved for use in the anaemia of chronic renal insufficiency [11, 12, 38]. The effects of dose and duration of therapy of rHuEPO on the rate of increase in PCV have been well described in this population. Adverse effects (thrombosis, accelerated hypertension, seizures) initially associated with the use of rHuEPO in this patient population are related to the excessively rapid correction of anaemia associated with larger doses of rHuEPO [44]; the dose in renal insufficiency has therefore been recommended as 50 $\mu g\ kg^{-1}$ s.c. three times weekly.

Anaemia associated with AIDS

rHuEPO has also been approved recently for treatment of the anaemia associated with AIDS. A prospective, randomized clinical trial demonstrated improvement of anaemia and reduction of transfusion requirements in patients undergoing zidovudine therapy, in whom initial serum concentrations of erythropoietin were less than 500 $\mu g\ ml^{-1}$ [13]. Six of 15 such patients were reported to develop anaemia requiring transfusion (haemoglobin concentration less than 10.0 $g\ dl^{-1}$) within a mean of 6 weeks of beginning zidovudine therapy, despite a nine-fold increase in endogenous erythropoietin concentrations [54]. As approximately 50 % of AIDS patients receiving zidovudine therapy have an anaemia associated with "lower" erythropoietin responses ($< 500\ \mu g\ ml^{-1}$) and zidovudine has been demonstrated recently to be useful in the treatment of paediatric AIDS patients [39], it is anticipated that rHuEPO therapy may be useful in this syndrome.

Other applications

Other possible applications for recombinant erythropoietin are under investigation for the treatment of the anaemia of chronic disease. Studies of endogenous serum concentrations of erythropoietin in patients with anaemia associated with cancer [40], chronic inflammatory disease [3] and AIDS [49] have shown that these diseases have erythropoietin responses inadequate for the degree of anaemia compared with patients with iron-deficient anaemia. Studies of anaemic patients with rheumatoid arthritis (an example of a relatively homogeneous patient group with chronic inflammation) have shown that rHuEPO therapy may be effective both for these patients [43] and in the anaemia of AIDS patients with "lower" erythropoietin responses [13]. Thus pharmacological doses of rHuEPO may be effective for anaemia previously thought to be attributable to environmentally related bone marrow factors rather than inadequate endogenous erythropoietin responses [8]. In addition to the anaemia of chronic inflammation, other potential applications of rHuEPO include anaemia related to cancer treated either without chemotherapy or with chemotherapy (in particular cis-platinum containing regimens, because of their nephrotoxic effects) [40].

rHuEPO may also be useful in the treatment of the anaemia of prematurity. For unexplained reasons, preterm infants may be unable to have an appropriate erythropoietic response in the face of a declining haemoglobin concentration [51]. Growing preterm infants have been demonstrated to have large numbers of circulating progenitor cells that are committed to erythroid differentiation; infant blood contains adequate numbers of responsive colonies of burst forming units-erythroid in *in vitro* culture systems [47]. Recent studies have demonstrated that bone marrow erythroid progenitor colonies are similarly responsive to recombinant erythropoietin in growing preterm infants with the anaemia of prematurity [45]. Thus the need for multiple donor transfusions of a specialized product such as cytomegalovirus-negative blood may be reduced or eliminated by rHuEPO therapy. Clinical trials to date have failed to demonstrate reduction of blood transfusion needs with rHuEPO in the neonate [46]; clinical trials using larger doses of rHuEPO are in progress.

Finally, erythropoietin responses in patients with sickle cell anaemia are known to be attenuated, with increases in serum concentrations of erythropoietin occurring only with haemoglobin concentrations of less than 9 g dl^{-1} [48]. Animal (baboon) studies have indicated that rHuEPO may stimulate a selective increase in percentage of fetal haemoglobin [1], so that rHuEPO therapy may have a potential for reducing the morbidity and frequency of the complications of intravascular sickling, such as vaso-occlusive crises. However, a trial of rHuEPO therapy accompanied by hypoxyurea therapy in patients with sickle cell anaemia failed to show any reduction in vaso-occlusive crises [17]. (For a more complete discussion of the structure and function of erythropoietin and of animal and clinical studies, the reader is referred to an excellent recent review [9].)

STIMULATION OF NON-ERYTHROID CELL LINES: COLONY STIMULATING FACTORS

The colony-stimulating factors (CSF) are a class of glycoprotein hormones that regulate the production and function of myeloid blood cells. Five of these factors—granulocyte–macrophage colony-stimulating factor (GM-CSF), granulocyte colony-stimulating factor (G-CSF), macrophage colony-stimulating factor (M-CSF), interleukin-3 (IL-3) and stem cell factor—have been cloned and the biosynthetic (recombinant) products are undergoing clinical trials. G-CSF and GM-CSF have been approved for use commercially and have important applications in the treatment or prevention, or both, of chemotherapy-induced neutropenia and in the treatment of cytopenias associated with diseases involving the bone marrow (myelodysplastic syndromes, aplastic anaemia, lymphoproliferative diseases, and congenital and idiopathic neutropenias). The rapidly evolving knowledge of this subject is expected to have significant implications for platelet and granulocyte transfusion needs in paediatric patients undergoing solid tumour and leukaemia chemotherapy or bone marrow transplantation, in HIV-infected patients undergoing myelosuppressive therapy, and in patients with congenital and idiopathic neutropenias.

GM-CSF

GM-CSF is a regulatory protein that stimulates proliferation, differentiation and maturation of myeloid haematopoietic precursors, including neutrophils, monocytes and eosinophils. In doses of less than 15 $\mu g\ kg^{-1}\ day^{-1}$, GM-CSF is tolerated well, but after larger doses patients begin to exhibit some toxicity, including bone pain, myalgia and rash. Studies of GM-CSF have shown benefit to patients undergoing autologous bone marrow transplantation, with accelerated recovery of neutrophil counts to more than 500 μl^{-1} within 14 days of transplant [2]. On the basis of subsequent randomized clinical trials of GM-CSF in patients with lymphoma undergoing autologous bone marrow transplantation, GM-CSF has recently been approved for commercial use. Extension of the use of this agent is anticipated in paediatric patients with chemotherapy-induced neutropenia, AIDS-induced neutropenia, aplastic anaemia and haematological malignancies (such as myelodysplastic syndromes and hairy cell leukaemia) [2].

G-CSF

G-CSF and GM-CSF differ in the spectrum of cells that bear their receptors, indicating that the clinical effects of these agents also probably differ. G-CSF exerts its strongest effects on granulocyte precursors, without exhibiting much influence on platelets or macrophages. As some of the toxicities associated with GM-CSF may be caused by activation of eosinophils and macrophages, the use of G-CSF may confer some advantage in a lower prevalence of side effects. Clinical studies of G-CSF in patients undergoing solid-tumour chemotherapy-induced neutropenia have shown that G-CSF decreased the extent and duration of neutropenia [15]. On the basis of subsequent randomized clinical trials of G-CSF in patients undergoing chemotherapy for solid tumours, G-CSF has been approved recently for commercial use. It is anticipated that use of this agent will be extended to paediatric patients with congenital agranulocytosis, cyclic neutropenia and HIV infection [2].

Other colony stimulating factors

Several haematopoietic growth factors, including GM-CSF, IL-3 and IL-6, are known to stimulate human megakaryocytopoiesis [5]. Further research and development of these growth factors and of stem cell colony-stimulating factor can be anticipated to have significant consequences for the platelet transfusion needs of patients, particularly in the areas of solid-tumour chemotherapy and bone marrow transplantation, and in the treatment of the leukaemias. Haematopoietic growth factors may be used in combination in clinical circumstances to achieve significant reductions in requirements for red blood cell and platelet transfusion support, and in morbidity and mortality caused by complications of infections.

REFERENCES

1. Al-Khatti A, Veith RW, Papayannopoulou T. Stimulation of fetal hemoglobin synthesis by erythropoietin in baboons. *New England Journal of Medicine* 1987; **317**: 415–420.
2. Appelbaum FR. The clinical use of hematopoietic growth factors. *Seminars in Hematology* 1989; (Suppl. 3): 7–14.
3. Baer AN, Dessypris EN, Goldwasser E, Krantz SB. Blunted erythropoietin response to anaemia in rheumatoid arthritis. *British Journal of Haematology* 1987; **66**: 559–564.
4. Bell K, Gillon J. Erythropoietin and preoperative autologous blood donation. *New England Journal of Medicine* 1990; **322**: 1157–1159.
5. Bruno E, Cooper RJ, Briddell RA, Hoffman R. Further examination of the effects of recombinant cytokines on the proliferation of human megakaryocyte progenitor cells. *Blood* 1991; 77: 2339–2346.
6. Egrie JC, Strickland TW, Lane J, Aoki K, Cohen AM, Smalling R, Trail G, Lin FK, Browne JK, Hines OK. Characterization and biologic effects of recombinant human erythropoietin. *Immunobiology* 1986; **172**: 213–224.
7. Erslev AJ. Humoral regulation of red cell production. *Blood* 1953; **8**: 349–357.
8. Erslev AJ. Erythropoietin coming of age. *New England Journal of Medicine* 1987; **316**: 101–103.
9. Erslev AJ. Erythropoietin. *New England Journal of Medicine* 1991; **324**: 1339–1345.
10. Erslev AJ, Caro J. Physiologic and molecular biology of erythropoietin. *Medical Oncology and Tumor Pharmacotherapy* 1986; **3**: 154–168.
11. Eschbach JB, Kelley MR, Haley NR. Treatment of the anemia of progressive renal failure with recombinant human erythropoietin. *New England Journal of Medicine* 1989; **32**: 158–163.
12. Eschbach JW, Egrie JC, Downing MR. Correction of the anemia of end-stage renal disease with recombinant human erythropoietin. Results of a combined phase I and II clinical trial. *New England Journal of Medicine* 1987; **316**: 3–78.
13. Fischl M, Galpin JE, Levine JD. Recombinant human erythropoietin for patients with AIDS treated with zidovudine. *New England Journal of Medicine* 1990; **322**: 1488–1493.
14. Friedman BA, Burns TL, Schork MA. An analysis of blood transfusion of surgical patients by sex: A quest for the transfusion trigger. *Transfusion* 1980; **20**: 179–188.
15. Gabrilove JL, Jacubowski A, Scher H, Sternberg C, Wong G, Grous J, Yagoda A, Fain K, Moore M, Clarkson B, Oettgen HF, Acton K, Welte K, Souza L. Effect of granulocyte colony-stimulating factor in neutropenia and associated morbidity due to chemotherapy for transitional-cell carcinoma of the urothelium. *New England Journal of Medicine* 1988; **318**: 1414–1422.
16. Gaudiani VA, Mason HDW. Preoperative erythropoietin in Jehovah's Witnesses who require cardiac procedures. *Annals of Thoracic Surgery* 1991; **51**: 823–824.
17. Goldberg MA, Brughara C, Dover GJ. Treatment of sickle cell anemia with hydroxyurea and erthropoietin. *New England Journal of Medicine* 1990; **323**: 366–372.
18. Goodnough LT. Erhythropoietic hormone: A review. In: Johnson RG, ed. *Blood Loss: Its Prevention and Replacement in Spine Surgery. Spine: State of the Art Reviews.* Philadelphia: Hanley and Belfus Inc., 1991; 109–118.
19. Goodnough LT. Erythropoietin as a pharmacologic alternative to homologous blood transfusion in the surgical patient. *Transfusion Medicine Reviews* 1990; **4**: 288–296.
20. Goodnough LT, Bravo J, Hsueh J, Keating L, Brittenham GM. Red blood cell volume in autologous and homologous blood units: implications for risk/benefit assessment for autologous blood "crossover" and direction blood transfusion. *Transfusion* 1989; **29**: 821–822.
21. Goodnough LT, Brittenham G. Limitations of the erythropoietic response to serial phlebotomy: implications for autologous blood donor programs. *Journal Laboratory and Clinical Medicine* 1990; **115**: 28–35.
22. Goodnough LT, Geha AS. A new era in blood conservation. *Annals of Thoracic Surgery* 1991; **151**: 703–704.
23. Goodnough LT, Johnston MFM, Toy PTYC. The variability of transfusion practice on coronary artery bypass graft surgery. *Journal of the American Medical Association* 1991; **265**: 86–90.
24. Goodnough LT, Marcus RE. Homologous blood transfusion needs in elective orthopaedic surgery: potential role of erythropoeitin therapy. *New England Journal of Medicine* 1990; **322**: 1158–1159.
25. Goodnough LT, Price TH, Rudnick S, Soegiarso RW. Preoperative red blood cell production in patients undergoing aggressive autologous blood phlebotomy with and without erythropoietin therapy. *Transfusion* 1992; **32**: 441–445.
26. Goodnough LT, Rudnick S, Price TH. Increased collection of autologous blood preoperatively with recombinant human erythropoietin therapy. *New England Journal of Medicine* 1989; **321**: 1163–1167.
27. Goodnough LT, Shaffron D, Marcus RE. The impact of preoperative autologous blood donation in elective orthopaedic surgery. *Vox Sanguinis* 1990; **59**: 65–69.
28. Goodnough LT, Shaffron D, Marcus RE. Utilization and effectiveness of autologous blood donation in arthroplastic joint surgery. *Journal of Arthroplasty* 1990; **5**: S89–S94.
29. Goodnough LT, Shuck J. Blood transfusion in elective surgery: Review of risks, options and informed consent. *American Journal of Surgery* 1990; **159**: 602–609.
30. Goodnough LT, Soegiarso RW. Surgical blood lost, the "transfusion trigger" and blood transfusions in coronary artery bypass graft surgery: implications for blood conservation strategies. *Clinical Research* 1992: **40**: 421A.
31. Goodnough LT, Wasman J, Corlucci K, Chernosky A. Limitations to donating adequate autologous blood prior to elective orthopaedic surgery. *Archives of Surgery* 1969; **124**: 494–496.
32. Hull A, Wasman J, Goodnough LT. The effects of an autologous blood education program on physician transfusion behaviour. *Academic Medicine* 1990; **65**: 681–685.
33. Kempen PM. Repeated blood donations and erythropoietin levels. *Journal of the American Medical Association* 1989; **261**: 1443.
34. Kickler TS, Spivak JL. Effect of repeated whole blood donations on serum immunoreative erythropoietin levels in autologous donors. *Journal of the American Medical Association* 1988; **260**: 65–67.
35. Kruskall MS, Glazer EE, Leonard SS, Willson SC, Pacini DG, Donovan LM, Ransil BJ. Utilization and effectiveness of a hospital autologous preoperative blood donor program. *Transfusion* 1986; **26**: 335–340.
36. Lee-Huang S. Cloning and expression of human erythropoietin cDNA in escherichia coli. *Proceedings of the National Academy of Sciences* USA 1984; **81**: 2708–2712.
37. Levine EA, Rosen AI, Gould SA. Recombinant human erythropoietin and autologous blood donation. *Surgery* 1988; **104**: 365–369.
38. Lim VS, DeGowin RI, Zavala D. Recombinant human erythropoietin treatment in pre-dialysis patients. *Annals of Internal Medicine* 1989; **110**: 108–114.
39. McKinney RE, Maha MA, Connor EM. A multicenter trial of oral zidovudine in children with advanced human immunodeficiency virus disease. *New England Journal of Medicine* 1991; **324**: 1018–1025.
40. Miller CB, Jones RJ, Piant Ados S. Decreased erythropoietin response in patients with the anemia of cancer. *New England Journal of Medicine* 1990; **322**: 1689–1692.
41. Miyake T, Kung CK, Goldwasser E. Purification of human erythropoietin. *Journal of Biological Chemistry* 1977; **252**: 5558–5564.
42. Owings DV, Kruskall MS, Thurer RL, Donovan LM. Autologous blood donations prior to elective cardiac surgery. Safety and effect on subsequent blood use. *Journal of the American Medical Association* 1989; **262**: 1963–1968.
43. Pincus T, Olsen NJ, Russell J. Multicenter study of recombinant human erythropoietin in correction of anemia in rheumatoid arthritis. *American Journal of Medicine* 1990; **89**: 161–168.
44. Raine AEG. Hypertensions, blood viscosity, and cardio-

vascular morbidity in renal failure: Implications for erythropoietin therapy. *Lancet* 1988; **1**: 97–99.
45. Rhondeau SM, Christensen RD, Ross MP. Responsiveness to recombinant human erthropoietin of marrow erythroid progenitors from infants with the "anemia of prematurity". *Journal of Pediatrics* 1988; **112**: 935–940.
46. Shannon KM, Mentzer WC, Abels RI. Recombinant human erythropoietin in the anemia of prematurity—results of a placebo-controlled pilot study. *Journal of Pediatrics* 1991; **118**: 949–955.
47. Shannon KM, Naylor GS, Torkildson JC. Circulating erythroid progenitors in the anemia of prematurity. *New England Journal of Medicine* 1987; **317**: 728–733.
48. Sherwood JB, Goldwasser E, Chilcote R. Sickle cell anemia patients have low erythropoietin levels for their degree of anemia. *Blood* 1986; **67**: 46–49.
49. Spivak SL, Barnes DC, Fuchs E, Quinn TC. Serum immunoreactive erythropoietin in HIV-infected patients. *Journal of the American Medical Association* 1989; **261**: 3104–3107.
50. Holland P, ed. *Standards for Blood Banks and Transfusion Services*, 13th Edn. Arlington VA: American Asssociation of Blood Banks, 1989; 40.
51. Stockman JA III. Erythropoietin: Off again, on again. *Journal of Pediatrics* 1988; **112**: 906–908.
52. Surgenor DM, Wallace El, Hao SHS, Chapman RH. Collection and transfusion of blood in the United States, 1982–1988. *New England Journal of Medicine* 1990; **322**: 1646–1651.
53. Toy PTCY, Strauss R, Stehling L. Predeposit autologous blood for elective surgery: A multicenter study. *New England Journal of Medicine* 1987; **316**: 517–520.
54. Walker RE, Parker RI, Kovacs JA. Anemia and erythropoiesis in patients with the Acquired Immunodeficiency Syndrome (AIDS) and Kaposi sarcoma treated with zidovudine. *Annals of Internal Medicine* 1988; **108**: 372–376.
55. Wasman J, Goodnough LT. Autologous blood donation for elective surgery. Effect on physician transfusion behavior. *Journal of the American Medical Association* 1987; **258**: 3135–3137.
56. Welch HG, Meehan KR, Goodnough LT. Prudent strategies for red blood cell transfusion. *Annals of Internal Medicine* 1992; **116**: 393–402.

British Journal of Anaesthesia 1993; **70**: 87–88

SHORT COMMUNICATIONS

INTRA-ARTICULAR MORPHINE FOR PAIN RELIEF AFTER ANTERIOR CRUCIATE LIGAMENT REPAIR

G. P. JOSHI, S. M. McCARROLL, O. H. BRADY, B. J. HURSON AND G. WALSH

SUMMARY

We have performed a randomized, double-blind controlled study in patients undergoing elective anterior cruciate ligament repair, to assess the effect of intra-articular morphine on postoperative pain. The morphine group ($n = 11$*) received morphine 5 mg in saline 25 ml and the control group (*$n = 9$*), saline 25 ml intra-articularly. Patients in the morphine group had significantly smaller pain scores throughout the 24-h postoperative period compared with those in the control group (*$P < 0.05$*). There was less requirement for supplementary analgesics in the morphine group.* (Br. J. Anaesth. 1993; **70**: 87–88)

KEY WORDS

Analgesia, postoperative. Analgesics: intra-articular morphine. Surgery: orthopaedic.

Reconstruction of the anterior cruciate ligament (ACL) of the knee is associated with a significant degree of postoperative pain. Effective analgesia can be obtained with the use of opioids by continuous extradural infusion or by patient-controlled analgesia (PCA). However, these techniques are not without significant side effects [1, 2] and they also require expensive equipment and monitoring.

Intra-articular opioids have been shown to provide high quality analgesia of long duration in patients undergoing arthroscopic procedures of the knee [3, 4]. The analgesia is mediated via a local action within the knee joint. However, the possibility that intra-articular opioids may provide postoperative analgesia in patients undergoing ACL reconstruction surgery has not been investigated and the aim of our study was to examine this.

METHODS AND RESULTS

After obtaining approval from the local Institutional Ethics Committee, we studied 20 consecutive patients (ASA I) undergoing elective ACL repair; all gave informed consent. In each case, the ACL repair was performed by the same surgeon using the same surgical technique.

Patients were premedicated with diazepam 0.15 mg kg^{-1} orally 2 h before surgery. Before premedication, patients were instructed in the use of a 10-cm visual analogue scale (VAS) with 0 and 10 labelled as "no pain" and "worst pain imaginable", respectively.

Anaesthesia was standardized: induction was with a sleep dose of thiopentone and fentanyl 2 μg kg^{-1} and anaesthesia was maintained with isoflurane and 70% nitrous oxide in oxygen. Tracheal intubation was facilitated with vecuronium and ventilation controlled mechanically. Monitoring included ECG, non-invasive arterial pressure, pulse oximetry and end-tidal carbon dioxide measurements. Residual neuromuscular block at the end of the surgery was antagonized with a mixture of neostigmine and glycopyrronium. At the conclusion of surgery, the patients were allocated randomly to two groups. Patients in the morphine group received preservative free morphine 5 mg in saline 25 ml, while those in the control group received normal saline 25 ml, both intra-articularly. The solution was injected after the knee joint was sealed and the tourniquet was released 10 min after the injection.

In the recovery room, after the patient's emergence from anaesthesia, an observer blinded to the agent injected recorded the VAS at 1, 2, 4, 8 and 24 h after operation. Patients who were asleep at the time of evaluation had no VAS recorded. Patients who complained of pain in the recovery room received papaveretum 2.5–5 mg i.v. every 5 min until the pain was controlled. On return to the ward, supplementary analgesia (papaveretum 0.2 mg kg^{-1} i.m.) was available on request. The severity (VAS) and the time of onset of pain were recorded by a blinded observer at the time of administration of analgesia. Patients were interviewed 24 h after operation. Results were analysed using the unpaired t test and the Mann–Whitney U test.

Of the 20 patients admitted to the study, 11 received intra-articular morphine and nine received saline injections. The two groups were similar in age, sex, weight, duration of surgery and amount of fentanyl administered during operation. The VAS scores in the morphine group were significantly ($P < 0.05$) smaller at all times as compared with the

---

G. P. JOSHI*, M.B., B.S., M.D., F.F.A.R.C.S.I.; S. M. MCCARROLL, M.B., B.A.O., B.CH., F.F.A.R.C.S.I.; O. H. BRADY†, M.B., B.A.O., B.CH., F.R.C.S.I.; B. J. HURSON, M.B., B.A.O., B.CH., M.CH., F.R.C.S.I.; G. WALSH, M.B., B.A.O., B.CH., F.F.A.R.C.S.I.; Cappagh Orthopaedic Hospital, Dublin, Ireland. Accepted for Publication: August 8, 1992.

Present addresses:

*Department of Anesthesiology, Oregon Health Sciences University, 3181 S.W. Sam Jackson Park Road, UHS-2, Portland, Oregon 97201-3098, U.S.A.

†Cork Regional Hospital, Ireland.

Correspondence to G. P. J. (Portland).

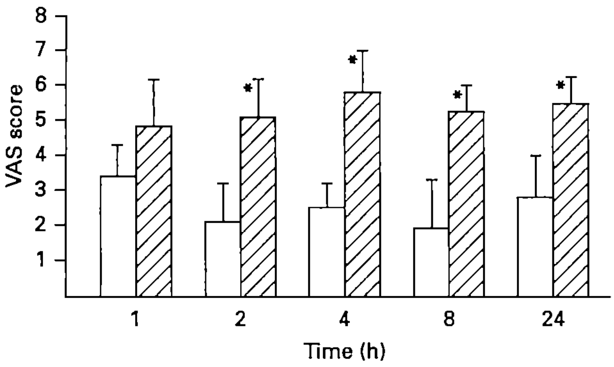


FIG. 1. Visual analogue scale (VAS) scores (mean, SEM) after the ACL repair in patients who received intra-articular morphine and saline. *Statistically significant difference between groups ($P < 0.05$). □ = Morphine group; ▨ = saline group (control).

control group (fig. 1). One patient in the study group required no analgesics and recorded VAS < 6 throughout the study. Patients in the morphine group required less papaveretum at all times. The mean (SEM) total requirement for papaveretum over the 24-h period was 52.7 (14.0) mg in the morphine group and 88.9 (17.6) mg in the control group ($P < 0.05$).

COMMENT

We have found that the use of intra-articular morphine in patients undergoing reconstructive surgery of the anterior cruciate ligament reduced the severity of postoperative pain significantly. Patients not only recorded significantly smaller pain scores, but also required less systemic analgesic.

Although the quality of analgesia overall was better and supplementary requirement of analgesics was reduced, there was a wide variation in pain scores and in analgesic requirements in the morphine group. One patient did not require any supplementary analgesia during the study period; this 24-yr-old female weighed 51 kg. The possibility arises that a larger dose or larger volume, or both, would be more effective in larger patients, suggesting that dose–response and volume–response relationships should be investigated. The dose and volume of the morphine used in this study were based on our previous experience with intra-articular morphine in arthroscopic knee surgery [3]. As patients who have ACL repair have the knee drained after operation, there is the possibility that a volume larger than 25 ml could be injected safely and may prove more effective. The other important component of this technique is to ensure that the tourniquet is kept inflated for at least 10 min after the intra-articular injection [3].

Other techniques used to relieve postoperative pain after ACL repair include continuous extradural infusion and i.v. PCA. However, these techniques are associated with side effects such as nausea, vomiting, pruritis and urinary retention [1]. Respiratory depression [5] and neurological damage, although rare, may also occur after extradural opioids. The incidence of urinary retention after extradural opioids in volunteers and patients varies from 0 to 90% [6]. As most patients undergoing ACL repair are young males, a high incidence of urinary retention would be expected.

The possibility arises that the action of morphine administered intra-articularly is via systemic absorption. We have shown in a previous study that the intra-articular administration of morphine results in very low plasma concentrations of morphine and its major metabolites [3]. The plasma concentrations of morphine recorded were less than 10 ng ml^{-1} throughout the sampling period—significantly less than those necessary for systemic analgesia. Systemic absorption effects would not explain the long duration of analgesia achieved after intra-articular injection.

REFERENCES

1. Etches RC. Complications of acute pain. In: Sandler AN, ed. *Anesthesiology Clinics of North America*. Philadelphia: W. B. Saunders, 1992; 417–433.
2. Thomas DW, Owen H. Patient controlled analgesia: the need for caution. *Anaesthesia* 1988; 43: 770–772.
3. Joshi GP, McCarroll SM, Cooney CM, Blunnie WP, O'Brien TM, Lawrence AJ. Intra-articular morphine for pain relief after knee arthroscopy. *Journal of Bone and Joint Surgery* 1992; 74B: 749–751.
4. Stein C, Comisel K, Haimeri E, Yassouridis A, Lehrberger K, Herz A, Peter K. Analgesic effect of intraarticular morphine after arthroscopic knee surgery. *New England Journal of Medicine* 1991; 325: 1123–1126.
5. Brockway MS, Noble DW, Sharwood-Smith GH, McClure JH. Profound respiratory depression after extradural fentanyl. *British Journal of Anaesthesia* 1990; 64: 243–245.
6. Petersen TK, Husted SE, Rybrol L, Schurizek BA, Wernberg M. Urinary retention during i.m. and extrdural morphine analgesia. *British Journal of Anaesthesia* 1982; 54: 1175–1178.

British Journal of Anaesthesia 1993; **70**: 89–91

USE OF ALFENTANIL WITH PROPOFOL FOR NASOTRACHEAL INTUBATION WITHOUT NEUROMUSCULAR BLOCK

S. F. E. COGHLAN, P. F. McDONALD AND G. CSEPREGI

SUMMARY

We have investigated the effect of augmentation of propofol with alfentanil for nasotracheal intubation without neuromuscular block in 60 patients undergoing short elective maxillo–facial procedures as outpatients. After administration of glycopyrronium 5 µg kg⁻¹ i.v., anaesthesia was induced with propofol 2.5 mg kg⁻¹, or alfentanil 20 µg kg⁻¹ and profopol 2.5 mg kg⁻¹. The alfentanil group had improved jaw relaxation ($P < 0.001$*) and vocal cord conditions (*$P < 0.005$*). Tracheal intubation was successful in 83% of patients receiving alfentanil, and in 73% of patients receiving propofol only. This difference was not significant. The cardiovascular response to intubation was attenuated in the alfentanil group.* (Br. J. Anaesth. 1993; **70**: 89–91)

KEY WORDS

Anaesthetics, intravenous: propofol. Analgesics: alfentanil. Intubation, nasotracheal: technique.

Patients undergoing short intraoral procedures often require nasotracheal intubation. Suxamethonium has significant side effects in patients rapidly returning to full mobility, while the use of atracurium and vecuronium for short procedures may delay discontinuation of anaesthesia. An induction dose of propofol depresses laryngeal reflexes, enabling laryngoscopy, and abducts and immobilizes the vocal cords. Alfentanil improves conditions for oral intubation using propofol without neuromuscular block [1] and prevents the haemodynamic response to instrumentation. This study was designed to see if augmentation of propofol with alfentanil improves conditions for nasotracheal intubation without neuromuscular block.

METHOD AND RESULTS

We investigated 60 adult patients requiring nasotracheal intubation for elective maxillo–facial surgery as outpatients. All patients were of ASA grade I or II and aged 16–55 yr. Hospital Ethics Committee approval and full written informed consent were obtained.

Patients were allocated randomly to two groups. Premedicant agents were not given. Measurements of mean arterial pressure, heart rate and arterial oxygen saturation were recorded at 1-min intervals from a Criticare 507 monitor. Recordings commenced before any pharmacological agents were given and continued until 3 min after tracheal intubation. Baseline values were taken 3 min after administration of glycopyrronium.

After cannulation of a large forearm vein, glycopyrronium 5 μg kg^{-1} was given and the lungs preoxygenated for 3 min. Group P received propofol 2.5 mg kg^{-1} and group A received propofol 2.5 mg kg^{-1} after administration of alfentanil 20 μg kg^{-1}. Propofol was infused at a rate of 200 mg min^{-1} using an Ohmeda 9000 (BOC) infusion pump. Depth of anaesthesia was assessed 30 s after completion of the infusion by loss of eyelash reflex and a negative response to verbal stimuli. A bolus of propofol 20 mg was given if induction was not complete, or if moving or coughing occurred during instrumentation. Further boluses of propofol were given if necessary. Laryngoscopy was performed in all patients, to see the vocal cords. The total dose of propofol and any response to instrumentation was noted. If intubation was unsuccessful after two attempts, suxamethonium 1 mg kg^{-1} was given.

Quality of intubation was scored according to two criteria: *Jaw relaxation* was classed according to a three-point scale: 1 = full relaxation, laryngoscopy easy; 2 = partial relaxation, laryngoscopy possible; 3 = laryngoscopy not possible.

The *position and movement of the vocal cords* were graded on a four-point scale: 1 = vocal cords abducted, no movement on intubation; 2 = vocal cords abducted but movement during intubation; 3 = vocal cords moving or adducted, intubation possible; 4 = intubation not possible.

Parametric data were analysed using Student's *t* test, paired within groups and unpaired between groups. Jaw relaxation compared class 1 with classes 2 and 3 using a four-fold chi-square test with Yates' correction. The state of the vocal cords was analysed using a two-tailed tie-corrected Mann–Whitney test. Failed intubation rates were compared using the Fisher exact probability test. Events during intubation were compared using "exact' confidence Binomial tables [2].

The two groups were comparable in age, sex and weight; each group comprised 30 patients. Mean dose of propofol to achieve intubation was 3.7 (SD

S. F. E. COGHLAN, M.B., CH.B., DIP.OBST.(OTAGO); P. F. McDONALD, M.B., CH.B., F.R.C.ANAES.; G. CSEPREGI, M.D., D.A.; Department of Anaesthesia, Walton Hospital, Rice Lane, Liverpool L9 1AE. Accepted for Publication: July 25, 1992.

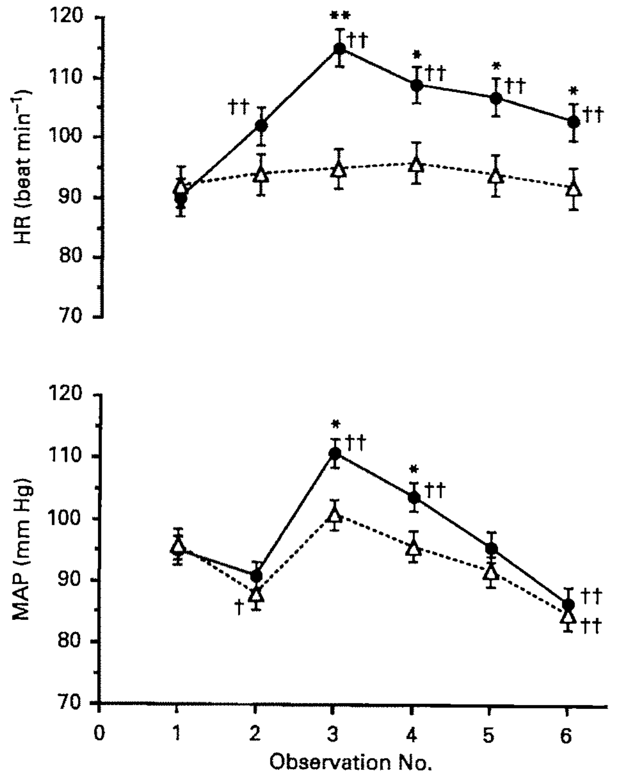


FIG. 1. Mean (SEM) changes in mean arterial pressure (MAP) and heart rate (HR) in patients receiving propofol alone (group P: ●), or with alfentanil (group A: △). Observations: 1 = Baseline; 2 = after induction; 3 = at intubation; 4–6 = 1, 2 and 3 min, respectively, after intubation. Significant differences between groups: $*P < 0.05$; $**P < 0.001$. Significant differences from baseline: $\dagger P < 0.05$; $\dagger\dagger P < 0.01$.

0.5) mg kg^{-1} in group P and 2.9 (0.5) mg kg^{-1} in group A ($P < 0.001$). Mean time to intubation was 157 (89) s in group P and 117 (84) s in group A (ns).

Two patients in group P were in class 1 and 28 in class 2 for jaw relaxation. In group A there were 15 patients in class 1, 13 in class 2 and two in class 3. Jaw relaxation was therefore improved in group A ($P < 0.001$). For vocal cord conditions, in group P there were two patients in grade 1, eight in grade 2, 12 in grade 3 and eight in grade 4. In group A there were 17 in grade 1, five in grade 2, three in grade 3 and five in grade 4. Vocal cord conditions were thus improved in group A ($P < 0.005$).

Intubation was successful in 22 (73%) of the patients in group P and 25 (83%) of the patients in group A (ns). Movement occurred in 28 (93%) of patients in group P and 14 (47%) in group A ($P < 0.01$). Coughing occurred in 29 (97%) of patients in group P and 19 (63%) of those in group A ($P < 0.01$).

In group P, there were significant increases from baseline values in mean arterial pressure and heart rate after intubation. In group A there was a small increase (ns) in mean arterial pressure and no change in heart rate (fig. 1).

COMMENT

We have investigated the potential for nasotracheal intubation without neuromuscular block using propofol either alone, or in combination with alfentanil. The depressant effects of benzodiazepines and topical lignocaine spray were thought to be unsuitable in a group of patients in whom the rapid return of these reflexes is required. All currently available myoneural blockers have undesirable properties when tracheal intubation is necessary for short procedures. Suxamethonium has well-documented side effects, and is tolerated poorly by outpatients. Vecuronium and atracurium, although of shorter duration than other non-depolarizing neuromuscular blockers in clinical use, may delay recovery from anaesthesia after short procedures.

Our results show that conditions for nasotracheal intubation were significantly better when propofol was augmented with alfentanil 20 μg kg^{-1}. Jaw relaxation was improved, vocal cord movement was reduced and the cords abducted. Coughing in response to intubation was decreased significantly, and the pressor response to intubation attenuated.

Keaveney and Knell [3] were successful in 95% of orotracheal intubations using propofol 2.5 mg kg^{-1} alone. Other studies, however, have achieved lower success rates, despite augmentation of propofol with a variety of alternative agents. Lignocaine 1.5 mg kg^{-1} i.v. was ineffective [4] and the combination of fentanyl 1.5 μg kg^{-1} and propofol 2–2.5 mg kg^{-1} provided poor intubating conditions [5].

Alfentanil, with its rapid onset and short duration of action, may be a logical choice of agent for augmenting propofol for short outpatient procedures. It effectively prevents the haemodynamic response to intubation. However, in a study comparing propofol and thiopentone for orotracheal intubation in patients pretreated with lignocaine 1.5 mg kg^{-1} and alfentanil 30 μg kg^{-1}, both groups had poor intubating conditions [6].

Saarnivaara and Klemola [1] assessed various doses of alfentanil in premedicated patients. They achieved an 86% success rate using alfentanil 30 μg kg^{-1} and propofol 2.5 mg kg^{-1}. This is similar to our own rate, despite use of a greater dose of alfentanil, a premedicant agent, and oral rather than nasal intubation.

Guidon-Attali and colleagues have published the only other study of nasotracheal intubation using propofol without neuromuscular block [7]. Patients were premedicated, an induction dose of propofol 3.5 mg kg^{-1} was given, and topical lignocaine spray was applied to the vocal cords and airway. The trachea of all patients was intubated successfully. We feel that the use of topical local anaesthesia is inappropriate when intraoral surgery is performed.

We have found that nasotracheal intubation was achieved readily with a combination of propofol and alfentanil in a group of young, unpremedicated outpatients. More completed intubations could probably have been peformed if more than two attempts at intubation had been made, but the authors felt that this would have compromised the safety of the technique. Other researchers have shown that topical local anaesthetic may further improve intubating conditions but, where this is contraindicated, the combination of propofol 2.5–3.0 mg kg^{-1} and alfentanil 20 μg kg^{-1} provides acceptable conditions for nasotracheal intubation in the majority of patients.

ACKNOWLEDGEMENTS

The authors thank Criticare U.K. for the loan of a printer and ICI Pharmaceuticals (U.K.) for aid with literature searching. Dr P. Charters has provided invaluable statistical and methodological advice.

REFERENCES

1. Saarnivaara L, Klemola UM. Intubating conditions and cardiovascular changes following induction of anaesthesia with propofol alone or in combination with alfentanil. *Acta Anaesthesiologica Scandinavica* 1989 **33** (Suppl.): 134.
2. Lenter C, Dieme K. *Geigy Scientific Tables*, 7th Edn. Macclesfied: Geigy Pharmaceuticals, 1971.
3. Keaveney JP, Knell PJ. Intubation under induction dose of propofol. *Anaesthesia* 1988; **43** (Suppl.): 80–81.
4. Mulholland D, Carlisle RJT. Intubation with propofol augmented with intravenous lignocaine. *Anaesthesia* 1991; **46**: 312–313.
5. Jacque JJ, Gold MI, Dehisser EA, Herrington C. Is propofol a muscle relaxant? *Anesthesia and Analgesia* 1990; **70** (Suppl.): S172.
6. Hovorka J, Honkavaara P, Kortilla K. Tracheal intubation after induction of anaesthesia with thiopentone or propofol without muscle relaxants. *Acta Anaesthesiologica Scandinavica* 1991; **35**: 326–328.
7. Guidon-Attali C, Mouillac F, Quilichini D, Paut O, Francois G. Propofol as the main anaesthetic agent in dental surgery. *Acta Anaesthesiologica Scandinavica* 1990; **34**: 397–399.

British Journal of Anaesthesia 1993; 70: 92–93

EFFECT OF ISOMETRIC THUMB PRELOAD ON THE EVOKED COMPOUND MUSCLE ACTION POTENTIAL

I. KALLI

SUMMARY

The effect of thumb preload on adductor pollicis muscle compound action potential (ECAP) was assessed after supramaximal ulnar nerve stimulus during steady isoflurane anaesthesia in 20 ASA I–II patients without neuromuscular block. During thumb preload, the peak-to-peak amplitude of the ECAP increased by 0.9 mV, to 9.5 (SD 2.2) mV ($P < 0.01$), because of the increased height of the negative half-wave. The positive half-wave amplitude did not change, but its duration was prolonged by 0.7 ms, to 6.4 (0.7) ms ($P < 0.05$). Consequently, there was a 15.9% increase in the area of the response curve ($P < 0.01$). Without preload, the first dorsal interosseus muscle peak-to-peak amplitude was 13.0 (4.3) mV. Thus thumb preload may not be the solution to improved monitoring of neuromuscular block by ECAP. (Br. J. Anaesth. 1993; **70**: 92–93)

KEY WORDS

Measurement techniques: neuromuscular junction, electrode position. Neuromuscular transmission: action potentials.

The evoked compound action potential (ECAP) may be recorded on the adductor pollicis muscle in order to monitor neuromuscular block. Electrical ulnar nerve stimulus first evokes an ECAP which is followed by a muscle contraction, but the two responses are different entities. Even so, it has been suggested that ECAP may be altered if constant isometric preload is applied to the muscle [1, 2].

The present investigation was designed to find out if preload applied to the thumb has any clinically notable effect on the ECAP recorded on adductor pollicis muscle.

METHODS AND RESULTS

The study was approved by the Ethics Committee of the Hospital and informed consent was obtained from the patients. We studied 20 healthy ASA I–II female patients (ages 35–50 yr, body weights 50–88 kg) with no disease and receiving no medication affecting the neuromuscular junction. The methods of anaesthesia, standardization of the study and ECAP recordings have been reported previously [3]. Nineteen of the patients had been included in the former study. One patient from that study was excluded because her isometric values were not measured, and she was replaced by another undergoing breast surgery.

The ECAP responses were recorded after a 30-min period of stabilization after induction of anaesthesia, during constant 0.5% (end-tidal) isoflurane and 67% nitrous oxide in oxygen anaesthesia without neuromuscular block. A neuromuscular relaxation monitor (Relaxograph, Datex, Finland) and a memory recorder (Hioki 8810, Hioki, Japan) were used.

The hand was supported in a splint. Initially, the thumb was not fixed and in a neutral position. Two of the disposable surface electrodes (Datex 57268) were positioned on the ulnar nerve. The ECAP was recorded with the active electrode on the motor point of the adductor pollicis muscle and the reference electrode on the second finger. The ground electrode was sited between the stimulus and recording electrodes (fig. 1).

In random order, the adductor pollicis ECAP was recorded without thumb pre-tension and with an isometric preload of 250 g. A calibrated spring dynanometer (155H, Pesola, Switzerland) was used

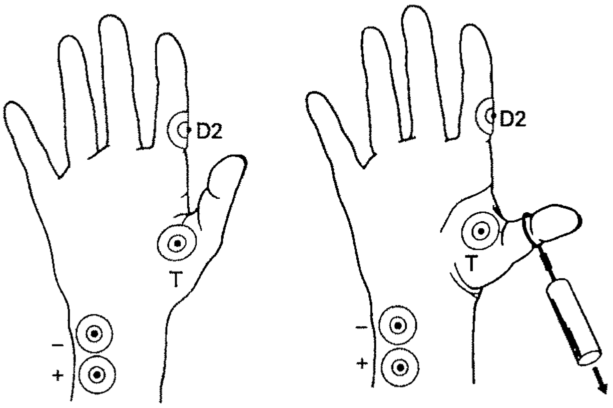


FIG. 1. For evoked compound muscle action potential recordings, the hand was fixed in a splint. Stimulus electrodes were positioned on the ulnar nerve at the wrist (+ and − indicate polarity). The active recording electrode (T) was located on the adductor pollicis muscle motor point. The reference recording electrode (D2) was on the proximal phalanx of the second finger. The ground was between the stimulus and recording electrodes. For the isometric recordings, the thumb was pulled with a constant preload of 250 g (right).

ILKKA KALLI, M.D., City Maternity Hospital, Department of Anaesthesia, Sofianlehdonkatu 5A, SF-00610 Helsinki, Finland.
Accepted for Publication: July 15, 1992.

to generate pre-tension, pulling the thumb to the static position opposite the contracting direction of the adductor pollicis muscle.

ECAP characteristics were analysed as described previously [3]. The first of the half-waves which pointed upwards was defined negative. The onset latency, the durations and amplitudes of the negative and positive half-waves, the peak-to-peak amplitude and curve area were measured.

The paired ECAP responses were compared using the Wilcoxon signed rank test. The results were regarded as statistically significant at $P < 0.05$.

A supramaximal response was obtained in all recordings. The finger skin temperature of the recorded hand varied in the range 32.4–34.7 °C.

When the paired ECAP responses were compared, there was no difference between the onset latencies or between the negative half-wave durations. During preload, the mean duration of the positive half-wave was prolonged by 0.7 ms, to 6.4 (0.7) ms ($P < 0.05$). The peak-to-peak amplitude increased to 9.5 (2.2) mV ($P < 0.01$) because of an increase in the height of the negative half-wave by 0.9 mV, to 5.6 (1.4) mV ($P < 0.001$). There was no significant change in the positive half-wave amplitudes.

There was a 15.9% increase ($P < 0.01$) in the total response curve area. The first dorsal interosseus muscle ECAP peak-to-peak amplitude of the 20 patients in the study was 13.0 (4.3) mV.

COMMENT

The ECAP may indeed be amplified slightly by applying preload to the thumb. This change may be a result of the altered recording electrode position in relation to the adductor pollicis muscle [4]. However, the amplitude of that amplified adductor pollicis response was only 73% of the interosseus muscle ECAP amplitude, which was recorded without any preload.

REFERENCES

1. Kopman A. The effect of resting muscle tension on the dose–effect relationship of d-tubocurarine: dose preload influence the evoked EMG. *Anesthesiology* 1988; **69**: 1003–1005.
2. Kalli I. Surface electrode positioning during ulnar nerve stimulation. *British Journal of Anaesthesia* 1991; **66**: 734–735.
3. Kalli I. Effect of surface electrode positioning on the compound action potential evoked by ulnar nerve stimulation during isoflurane anaesthesia. *British Journal of Anaesthesia* 1990; **65**: 494–499.
4. Wee AS, Ashley RA. Effect of thumb position on thenar compound muscle action potential. *Electromyography and Clinical Neurophysiology* 1988; **28**: 163–166.

British Journal of Anaesthesia 1993; 70: 94–95

GLYCOPYRRONIUM PROLONGS TOPICAL ANAESTHESIA OF ORAL MUCOSA AND ENHANCES ABSORPTION OF LIGNOCAINE

H. WATANABE, L. LINDGREN, P. ROSENBERG AND T. RANDELL

SUMMARY

We have studied the effect of glycopyrronium on the anaesthetic action and absorption of topical lignocaine in 10 healthy, non-smoking volunteers. Lignocaine 100 mg was sprayed on the oral mucosa 15 min after random administration of glycopyrronium 4 μg kg^{-1} or normal saline i.v. Glycopyrronium decreased the mean analgesia score from 2 to 0.1 (2 = baseline; 0 = anaesthesia) at 4 min compared with a change from 2 to 0.5 after normal saline ($P < 0.05$). All scores returned to baseline by 40 min and 20 min in the glycopyrronium and control groups, respectively. The mean (SD) peak plasma lignocaine concentration was 0.57 (0.29) μg ml^{-1} after glycopyrronium and 0.31 (0.10) μg ml^{-1} after saline ($P < 0.05$) and were attained in 17 min (range 10–40 min) and 29 min (range 8–40 min), respectively. Pretreatment with glycopyrronium enhanced absorption and prolonged the analgesic action of topically administered lignocaine. (Br. J. Anaesth. 1993; **70**: 94–95)

KEY WORDS

Anaesthetic techniques: topical. Anaesthetics, local: lignocaine. Anticholinergics: glycopyrronium.

Topical anaesthetics are often applied to mucous membranes of the airway before laryngoscopy or bronchoscopy [1–3]. The plasma concentrations of lignocaine vary after topical administration [1–4] and absorption is affected by the site and method of administration [3, 5]. It has been suggested that the anaesthetic efficacy and plasma concentrations of a topical local anaesthetic may be affected also by the conditions of the mucous membranes [1, 3, 5].

An anticholinergic agent may be administered before procedures in the mouth and upper airway to inhibit vagal responses and to dry mucous membranes. The present study was designed to evaluate the effect of i.v. glycopyrronium on duration of analgesia and plasma concentrations after topical administration of lignocaine.

METHODS AND RESULTS

After obtaining hospital Ethics Committee approval, we studied 10 healthy, non-smoking volunteers (five females and five males, ages 19–47 yr, weights 55–100 kg) in a randomized fashion. Each subject served as their own control. At least 24 h elapsed between each experiment.

Subjects were studied in the supine position with a 30° head-up tilt. An antecubital vein was cannulated for i.v. administration of drugs and for obtaining blood samples for measurement of plasma concentrations of lignocaine.

After baseline measurements, either glycopyrronium 4 μg kg^{-1} or normal saline was injected in the same volume over 30 s. Before the experiment, the solutions were prepared in coded syringes by a nurse. The i.v. cannula was flushed with 2 ml of normal saline.

The antisialagogue effect was assessed at 1, 2, 3, 5, 10 and 15 min after administration of the solution using a 0–10 visual analogue scale (VAS): 0 = very dry mouth; 10 = very wet mouth. The time elapsed from drug administration to the point when the subject indicated dryness of the mouth was recorded.

Fifteen minutes after drug administration, the subjects inhaled and held their breath, then lignocaine 100 mg (Xylocain, Astra, Sweden) was sprayed over 10 s on the buccal surfaces and the upper part of the soft palate. Subjects were allowed to swallow, but not to spit. Sensation to pinprick in the soft palate was assessed and scored: 0 = no sensation (anaesthesia); 1 = feeling of touch only (analgesia); 2 = normal sensation (baseline). These tests were performed by the same investigator, who was unaware of the dryness score given by the subject.

During the study the ECG was monitored continuously. Heart rate (HR) and arterial pressures (AP) were recorded every 5 min until lignocaine spray. After the spraying, HR and AP were recorded, analgesia tested and blood obtained at 2, 4, 6, 8, 10, 15, 20, 30 and 40 min. Any symptoms of lignocaine toxicity were noted.

Blood samples for measurement of plasma concentrations of lignocaine were obtained in tubes containing dried lithium heparin. After centrifugation, samples were frozen. Lignocaine concentrations

---

H. WATANABE, M.D., Department of Anesthesiology, Sapporo Medical College, Sapporo, Japan. L. LINDGREN†, M.D.; P. ROSENBERG, M.D.; Department of Anaesthesia, 4th Department of Surgery, Kasarmikatu 11-13, 00130 Helsinki, Finland. T. RANDELL, M.D., Department of Anesthesia, College of Medicine, University of Iowa, Iowa City, Iowa, U.S.A. Accepted for Publication: August 27, 1992.

Correspondence to L. L.

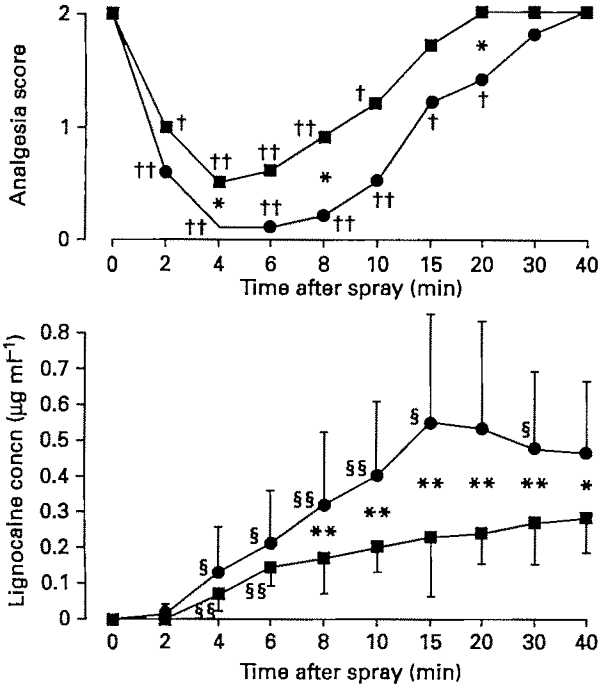


FIG. 1. Analgesia scores (0 = anaesthesia; 1 = analgesia; 2 = baseline) and the plasma concentrations of lignocaine. Time 0 = baseline. ● = Glycopyrronium group; ■ = control group. Significant differences between groups: $^{*}P < 0.05$; $^{**}P < 0.01$. Significant differences within the groups compared with baseline: $\dagger P < 0.05$; $\dagger\dagger P < 0.01$. Significant differences within the groups compared with previous point: $\S P < 0.05$; $\S\S P < 0.01$.

were measured by gas chromatography [6] after completion of the study.

Data were analysed by Wilcoxon signed rank test with $P < 0.05$ considered statistically significant.

After glycopyrronium, the VAS score indicating the degree of dryness of the mouth decreased gradually from mean 6.7 (range 5–10), to 4.3 (2–6) at 15 min ($P < 0.01$). Subjects noted increasing dryness of the mouth 7 min (range 2–15 min) after injection. After saline, the score did not change significantly from baseline (6.9 (5–10)) and none of the subjects reported dryness. During the study, nine of 10 subjects receiving glycopyrronium and six of 10 subjects receiving saline scored sensation to pinprick as 0 (fig. 1).

Mean (SD) peak plasma concentration of lignocaine was 0.57 (0.29) µg ml^{-1} after glycopyrronium and 0.31 (0.10) µg ml^{-1} after saline ($P < 0.05$). The greatest individual lignocaine concentrations were 1.2 µg ml^{-1} and 0.48 µg ml^{-1}, respectively, reached in 17 min (range 10–40 min) and 29 min (range 8–40 min) ($P < 0.05$) (fig. 1). Peak lignocaine concentrations and body weight did not correlate (correlation coefficients: 0.11 in both groups). There were no side effects in any subjects after lignocaine.

Mean (SD) HR increased from 70 (14) beat min^{-1} at baseline to 78 (16) beat min^{-1} at 15 min ($P < 0.05$) and 83 (19) beat min^{-1} 2 min after lignocaine ($P < 0.01$) in subjects receiving glycopyrronium. After saline, HR increased in response to lignocaine, from 68 (10) beat min^{-1} to 76 (19) beat min^{-1} ($P < 0.05$). At 15 min after drug administration, the difference in HR between groups was significant ($P < 0.01$). AP did not change significantly in either group.

COMMENT

It has been suggested that anticholinergic drugs, by drying the mouth, increase the degree of topical anaesthesia [5]. In this study, we found that analgesia scores were on average smaller and the duration of analgesia clearly longer after administration of glycopyrronium.

Absorption of lignocaine through the mucous membranes of the airway is rapid and depends not only on the characteristics of the drug, but also on the site of application, being more rapid from the lower than from the upper airway [5]. Efthimou and colleagues showed that only 5 % of variation in the absorption of lignocaine was attributable to sputum volume or cigarette consumption. The most important factor was the dose per unit body weight [3]. We did not find a positive correlation between the maximal concentration of lignocaine and the dose given, but our results indicate that anticholinergic drugs may enhance topically administered lignocaine absorption. This contradicts results of Morrell, Chappell and White [1]. Their study was not, however, focused on the effect of anticholinergics on lignocaine absorption.

The time to reach peak concentrations after topical lignocaine administration has been found to vary [1–4]. Efthimiou and colleagues sprayed lignocaine on the oral mucosa of unpremedicated volunteers. The dose was larger than ours, but the value of absorption was similar to our control data [3]. Absorption was significantly faster after glycopyrronium in our study. Without anticholinergic pretreatment, topical anaesthetic is diluted and washed by saliva, decreasing contact with the oral mucosa and increasing the amount swallowed. The swallowed lignocaine is probably absorbed slowly in the duodenum, perhaps explaining the slowly increasing and small plasma concentrations.

ACKNOWLEDGEMENT

We thank Ms Aira Alila for laboratory assistance and the Paulo Foundation, Finland, for financial support.

REFERENCES

1. Morrell DF, Chappell WA, White IWC. Topical analgesia of the upper airway with lignocaine. *South African Medical Journal* 1982; **10**: 551–553.
2. Patterson JR, Blaschke TF, Hunt KK, Meffin PJ. Lidocaine blood concentrations during fiberoptic bronchoscopy. *American Review of Respiratory Disease* 1975; **112**: 53–57.
3. Efthimiou J, Higenbottam T, Holt D, Cochrane GM. Plasma concentrations of lignocaine during fiberoptic bronchoscopy. *Thorax* 1982; **37**: 68–71.
4. Rosenberg PH, Heinonen J, Takasaki M. Lidocaine concentration in blood after topical anaesthesia of the upper respiratory tract. *Acta Anaesthesiologica Scandinavica* 1980; **24**: 125–128.
5. Ovassapian A. Topical anesthesia of the airway. In: Ovassapian A, ed. *Fiberoptic Airway Endoscopy in Anesthesia and Critical Care*. New York: Raven Press, 1990; 45–56.
6. Mather LE, Tucker GT. Meperidine and other basic drugs: general method for their determination in plasma. *Journal of Pharmacological Science* 1974; **63**: 306–307.

British Journal of Anaesthesia 1993; **70**: 96–98

HAEMODYNAMIC AND METABOLIC CONSEQUENCES OF AORTIC OCCLUSION DURING ABDOMINAL AORTIC SURGERY

D. G. WHALLEY, F. C. SALEVSKY AND J. V. RYCKMAN

SUMMARY

We have studied the haemodynamic and metabolic effects of application and removal of the infrarenal aortic crossclamp in 20 patients during aortic reconstructive surgery for repair of aneurysmal or occlusive disease. A highly significant positive correlation was detected between the change in systemic vascular resistance (SVR) associated with application of the aortic crossclamp and the change in base deficit (BD) associated with its removal ($r = 0.851$; $P = 0.001$). There was no difference in regression analysis ($P = 0.21$) or mean change of SVR and BD ($P = 0.73$) in patients with either aneurysmal or occlusive disease. In addition, the maximum increase in mixed venous serum lactate concentration correlated positively with the duration that the aortic crossclamp was applied ($r = 0.717$, $P = 0.0297$). These observations suggest the importance of the collateral circulation in the development of metabolic acidosis during aortic surgery. (Br. J. Anaesth. 1993; **70**: 96–98).

KEY WORDS

Acid–base equilibrium: base deficit. Arterial pressure: systemic vascular resistance. Surgery: aortic.

Application of an infrarenal aortic crossclamp during aortic reconstructive surgery may be associated with substantial increases in systemic vascular resistance and arterial pressure which, in patients with coronary artery disease, may further compromise cardiac performance by increasing myocardial wall tension [1]. There is evidence that patients undergoing aortic reconstructive surgery for occlusive disease experience smaller increases in systemic vascular resistance at the time the crossclamp is applied than those patients with aneurysmal disease, presumably because of better developed collateral vascularization in the former [2], but these data conflict with the experience of other workers who have found no such distinction [3]. Cunningham and colleagues were unable to demonstrate differences in the immediate haemodynamic consequences of crossclamping the aorta between patients with occlusive or aneurysmal disease, but noted that the extent of collateral circulatory changes associated with occlusive disease influenced the magnitude of haemodynamic changes during the period the aorta was crossclamped [3].

Studies of the metabolic effects of aortic reconstructive surgery have demonstrated increases in Pa_{CO_2} and venous serum lactate concentrations after release of the aortic crossclamp, but no consistent change in pH [4, 5]. The increase in serum lactate concentration begins during the time the aorta is crossclamped and persists into the immediate postoperative period, suggesting that the metabolic consequences of peripheral ischaemia begin at the time of application of the aortic crossclamp or shortly thereafter [4].

The hypothesis of the present study was that the immediate haemodynamic changes associated with application of the aortic crossclamp during aortic reconstructive surgery reflect the degree of collateral vascularization [2, 3] and therefore the degree of peripheral ischaemia, irrespective of whether the patient has occlusive or aneuysmal disease, and that the magnitude of such changes predicts the subsequent metabolic disturbances that occur after removal of the crossclamp. We have therefore examined the relationship between haemodynamic and metabolic changes during aortic surgery.

METHODS AND RESULTS

In a prospective study approved by the local Ethics Committee, we have made observations in 20 patients (17 male) undergoing infrarenal aortic reconstructive surgery. The aorta was aneurysmal in 12 patients and in the remaining eight patients surgery was undertaken for correction of atherosclerotic occlusive disease. Mean age of the patients was 70.3 yr and mean (SD) height, weight and BSA were 174.7 (9) cm, 76.4 (15.3) kg and 1.88 (0.26) m^2, respectively. Patients received their usual cardiovascular medication before surgery, and premedication with either diazepam 5 mg orally or midazolam 1–2 mg i.v. Before induction of anaesthesia, i.v., i.a. and thermodilution pulmonary artery catheters were inserted under local anaesthesia and control haemodynamic variables measured. These included heart rate, mean arterial pressure (MAP), systemic vascular resistance (SVR), cardiac output (CO), central venous pressure and pulmonary capillary wedge pressure (PCWP).

Anaesthesia was induced with fentanyl 10 $\mu g\ kg^{-1}$ and a sleep dose of thiopentone followed by pan-

---

D. G. WHALLEY, M.B., CH.B., F.R.C.ANAES., F.R.C.P.C.; J. V. RYCKMAN, M.D.; Department of General Anesthesiology, The Cleveland Clinic Foundation, 9500 Euclid Avenue, M-26, Cleveland, OH 44195 U.S.A. F. C. SALEVSKY, B.SC., M.SC., M.D., F.R.C.P.C., Department of Anaesthesia, Royal Victoria Hospital, 687 Pine Avenue West, Montreal, Quebec H3A 1A1, Canada.
Accepted for Publication: August 4, 1992.

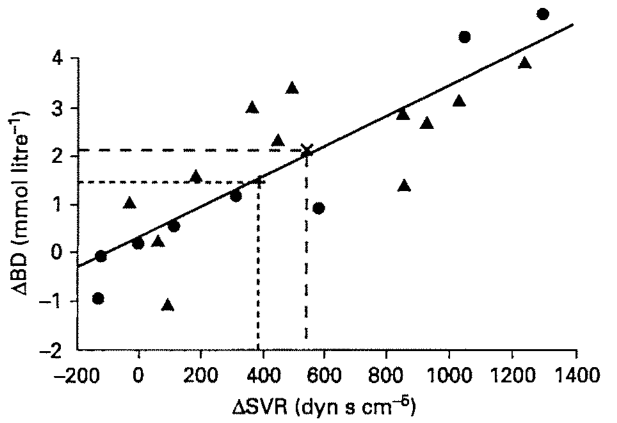


FIG. 1. Relationship between change in SVR from before to after application of the aortic crossclamp (ΔSVR) and change in base deficit from before to after release of the aortic crossclamp (ΔBD) in patients with aneurysmal disease (▲) or occlusive disease (●). —x— = Mean ΔSVR and mean ΔBD for patients with aneurysmal disease; ---+--- = mean ΔSVR and mean ΔBD for patients with occlusive disease. $r = 0.851$; $P = 0.0001$.

curonium 0.1 mg kg^{-1} to facilitate tracheal intubation. Anaesthesia was maintained with nitrous oxide in oxygen, enflurane to an end-tidal concentration of 0.5–1.5 % and periodic administration of pancuronium 1 mg to prolong neuromuscular block. Ventilation was adjusted to $P\text{E}'_{CO_2}$ 3.32–3.99 kPa immediately after induction and was not altered during surgery.

Ringer's lactate and packed red cells were given i.v. to maintain the PCWP at pre-induction values and the PCV > 25 %.

Patients' lungs were ventilated during the immediate postoperative period until the pulmonary artery temperature was > 36 °C, whereupon they were considered suitable for tracheal extubation.

Additional haemodynamic variables were obtained periodically during surgery, but specifically, immediately before and within 5 min after application of the aortic crossclamp and immediately before and 15 min after removal of the aortic crossclamp. Mixed venous and arterial blood-gas analysis, mixed venous serum lactate concentrations and end-tidal carbon dioxide measurements were obtained before induction of anaesthesia, before and after application of the aortic crossclamp, before and after removal of the aortic crossclamp and at 5 min, 10 min and 15 min after unclamping.

Using linear regression analysis, the maximum changes in mixed venous serum lactate concentrations, mixed venous $P\text{CO}_2$ and extracellular fluid base deficit were correlated with the duration that the aorta was crossclamped (range 20–92 min) and the change in MAP, SVR and CO associated with application of the aortic crossclamp. The base deficit (BD) was derived from the standard bicarbonate (HCO_3) and pH ($BD = 24 - HCO_3 + 12\ [7.4 - pH]$) and the correlations were considered significant at $P < 0.05$ [6].

A highly significant positive correlation was demonstrated between the base deficit revealed after the crossclamp was removed and the increase in SVR associated with application of the crossclamp ($r = 0.851$, $P = 0.0001$; $\Delta BD = 0.36 + 0.003\ [\Delta SVR]$) (fig. 1). There was a trend to a significant relationship between the changes in venous serum lactate and SVR ($P = 0.09$), but there was a significant difference between the change in venous serum lactate concentration and the duration of aortic crossclamp ($r = 0.717$, $P = 0.0297$; $\Delta\text{lactate} = -0.64 + 0.038$ [duration of aortic crossclamp]). No other correlation was significant.

The data were analysed further to determine if the significant relationship between ΔBD and ΔSVR differed for those patients with aneurysmal or occlusive disease. Regression lines were constructed for both groups, but analysis of covariance showed no interaction ($P = 0.16$) and no difference ($P = 0.21$). Furthermore, subsequent analysis using the Hotelling's T^2 test for simultaneous comparison of continuous, dependent data revealed no difference between the groups in the mean ΔBD and mean ΔSVR (mean (SD): aneurysm group ΔBD 2.11 (1.4) mmol litre^{-1}, ΔSVR 539.25 (427.7) dyn s cm^{-5}; occlusive group ΔBD 1.45 (2.1) mmol litre^{-1}, ΔSVR 379.9 (541.7) dyn s cm^{-5}) ($P = 0.73$), suggesting that under the conditions of the study the two groups were from the same patient population.

COMMENT

We have demonstrated a significant relationship between the haemodynamic effects expressed as a change in SVR associated with the application of the aortic crossclamp and the subsequent metabolic acidosis expressed as an increase in base deficit revealed after the crossclamp was removed. Furthermore, the increase in mixed venous serum lactate concentrations was related directly to the duration of aortic crossclamp. These observations suggest that it is the patency of the collateral circulation as reflected in the haemodynamic changes at the time of crossclamp that governs the degree of anaerobic metabolism suffered by the partially ischaemic tissues during the time the aorta is occluded, and the subsequent metabolic acidosis revealed upon reperfusion.

We have measured the blood-gas tensions and serum lactate concentrations in mixed venous blood to determine more accurately the acid–base status of the tissues and we have confirmed the metabolic changes during aortic reconstructive surgery described by others [4, 5]. $P\bar{v}_{CO_2}$ and pH consistently increased and decreased, respectively, upon release of the crossclamp, but the magnitude of the changes was too variable to correlate significantly with the haemodynamic changes.

The mixed venous serum lactate concentration began to increase shortly after application of the aortic crossclamp and the increase continued while the crossclamp was in place. This observation is in agreement with that of Anderrson and colleagues, who, in addition, described further increases in venous serum lactate concentration 60 min after removal of the crossclamp [4]. However, the increases in the present study did not correlate with haemodynamic changes, suggesting that serum lactate concentration is a more sensitive indicator of the adequacy of oxygen delivery than alteration in SVR.

In contrast with Johnson and colleagues [2], we were unable to distinguish between the haemodynamic changes associated with application of the aortic crossclamp in patients with aneurysmal disease and those with occlusive disease. There was no difference in the mean change in SVR between the two groups of patients at the time of aortic crossclamp, suggesting a similar degree of collateral circulation in each group and an overlap of the disease process. Furthermore the relationship between ΔSVR and ΔBD was similar for both groups. Although the sample size was small, the regression lines for each group showed significant correlation, but no interaction and no statistical difference between them.

ACKNOWLEDGEMENTS

The authors acknowledge the statistical advice of Miss Lisa Gragg.

REFERENCES

1. Attia RR, Murphy JD, Snider M, Lappas DG, Darling RC, Lowenstein E. Myocardial ischaemia due to infrarenal aortic crossclamping during aortic surgery in patients with severe coronary artery disease. *Circulation* 1976; **53**: 961–967.
2. Johnson WE, Balestrieri FJ, Plonk G, D'Souza V, Howard G. The influence of periaortic collateral vessels on the intraoperative hemodynamic effects of acute aortic occlusion in patients with aorto-occlusive disease or abdominal aortic aneurysm. *Anesthesiology* 1987; **66**: 386–389.
3. Cunningham AJ, O'Toole DP, McDonald N, Keeling F, Bouchier-Hayes D. The influence of collateral vascularization on haemodynamic performance during abdominal aortic surgery. *Canadian Journal of Anaesthesia* 1989; **36**: 44–50.
4. Anderrson J, Eklof B, Neglen P, Thomson D. Metabolic changes in blood and skeletal muscle in reconstructive aortic surgery. *Annals of Surgery* 1979; **189**: 283–289.
5. Falk JL, Rackow EC, Blumenberg R, Gelfand M, Fein IA. Hemodynamic and metabolic effects of abdominal aortic crossclamping. *American Journal of Surgery* 1981; **142**: 174–177.
6. Collier CR, Hackney JD, Mohler JG. Use of extracellular base excess in diagnosis of acid–base disorders: a conceptual approach. *Chest* 1972; **61**: 6S–10S.

British Journal of Anaesthesia 1993; **70**: 99–100

PROPOFOL DECREASES RANDOM AND CHEMOTACTIC STIMULATED LOCOMOTION OF HUMAN NEUTROPHILS *IN VITRO*

A. G. JENSEN, C. DAHLGREN AND C. EINTREI

SUMMARY

We have studied the influence of clinical concentrations of propofol (2,6-diisopropyl phenol), emulsified propofol (Diprivan) and the emulsifier of propofol (Intralipid 10%) on random and chemotactic locomotion of human polymorphonuclear leucocytes in an agarose assay. Random locomotion was decreased ($P < 0.001$) to a similar extent by the three drugs. Concentrations of propofol 2.5 μg ml^{-1} and greater, and of Diprivan 3.33 μg ml^{-1} and greater, also reduced chemotaxis ($P < 0.05$) against both zymosan-activated human serum (C5a) and N-formyl-methionyl-leucyl-phenylalanine (FMLP), used as chemoattractants. Intralipid reduced chemotaxis towards C5a but not towards FMLP. We conclude that propofol in clinically relevant concentrations may adversely affect leucocyte locomotion in vitro. (Br. J. Anaesth. 1993; **70**: 99–100)

KEY WORDS

Anaesthetics, intravenous: propofol. Blood: leucocytes. Toxicity: leucocyte chemotaxis.

Anaesthetics may compromise host defence mechanisms by adversely affecting the specific or non-specific components of the normal immune response. The migration of neutrophils is one of the earliest events in the body's non-specific defence against infection. Adverse effects of general anaesthetic agents on neutrophil function *in vitro* are important as, theoretically, they could imply compromised function *in vivo*; a depressed immune response after anaesthesia may lead to an increased incidence of postoperative infections.

We have investigated the effect of propofol on the random and chemotactic locomotion of human polymorphonuclear neutrophils. Propofol, in the clinically used preparation 10 mg ml^{-1}, is dissolved in a fat emulsion with a composition identical to that of Intralipid 100 mg ml^{-1} (Kabi Vitrum, Stockholm, Sweden). It is known that Intralipid depresses both random and directed locomotion of neutrophilic granulocytes [1]. To study the effect of both the emulsifier and the active drug, we investigated the effects of Diprivan and used both pure propofol and Intralipid as controls.

METHODS AND RESULTS

Venous blood was obtained from 15 healthy adult volunteers and neutrophils were separated from heparinized blood using standard techniques [2]. Agarose (Litex, Copenhagen, Denmark) was dissolved in 60 ml of water by heating (1.2% w/v). After temperature equilibration, equal volumes of the agarose solution and of double-concentrated Geys medium and 2% human serum albumin were mixed. This solution was supplemented and mixed with the drug under investigation and poured into tissue culture dishes (60 × 13 mm; Flow, Edinburgh, Scotland). Twelve holes were cut in the agarose using a specially constructed mould. After addition of 10 μl of normal human serum containing zymosan (C5a) 5 mg ml^{-1} to two of the holes in each plate, the plates were incubated for 1 h at 37 °C in 5% carbon dioxide. Ten microlitre of the cells was added to the six holes in the centre of the plate and 10 μl of N-formyl-methionyl-leucyl-phenylalanine (FMLP) 10^{-7} mol litre^{-1} was added to two of the holes at the periphery. The plates were then incubated for 60 min under the same conditions as before. The cells were fixed in 3.7% cold formalin, and stained with Giemsa.

The migration distance was measured under a microscope, measuring on an arbitrary scale the distance from the edge of the well to the leading front of neutrophils [3]. The mean and SD of at least 12 readings were calculated for each concentration and drug. The significance of the difference in migration in arbitrary scale units between the control cells and the cells treated with different drugs and different concentrations was assessed by Student's t test. $P < 0.05$ was considered significant.

The effects on granulocyte locomotion of four different concentrations of Diprivan were studied: 1.66 μg ml^{-1}, 2.5 μg ml^{-1}, 3.33 μg ml^{-1} and 33.3 μg ml^{-1}. Random locomotion was reduced significantly by Diprivan—by about 50% for all the concentrations used. Directional locomotion towards

---

ANDERS GADEGAARD JENSEN, MD., D.E.A.A.; CHRISTINA EINTREI, M.D., PH.D.; Department of Anaesthesiology, Faculty of Health Sciences, Linköping University Hospital, S-581 85 Linköping, Sweden. CLAES DAHLGREN, PH.D., Department of Medical Microbiology and Immunology, University of Göteborg, S-413 46 Göteborg, Sweden. Accepted for Publication: August 18, 1992.

Correspondence to A. G. J.

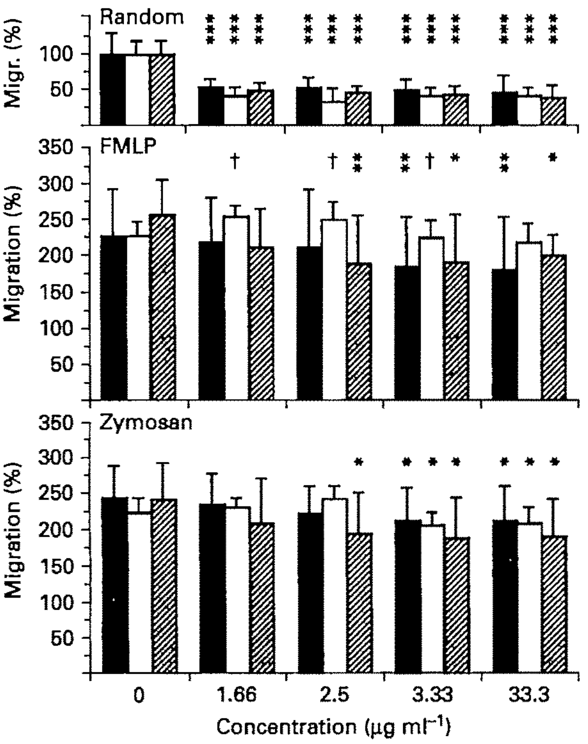


FIG. 1. Mean (SD) locomotion of leucocytes at random and after stimulation with FMLP and zymosan (C5a), at different concentrations of Diprivan (■) propofol (▨) and Intralipid (☐) (concentrations of Intralipid 10 times greater than noted). 100% migration = distance of random migration in controls without drug. Significant differences: $*P < 0.05$, $**P < 0.01$ and $***P < 0.001$—compared with respective migration at concentration 0; $\dagger P < 0.05$—Intralipid compared with Diprivan and propofol.

FMLP and C5a was reduced to a similar degree with Diprivan 3.33 µg ml^{-1} and 33.3 µg ml^{-1}. Reduction of random locomotion was more pronounced than the reduction observed after chemoattractants (fig. 1).

The results using propofol were similar to those with Diprivan, as random locomotion was reduced by all the concentrations investigated. Directed locomotion in response to both FMLP and C5a was significantly reduced with concentrations of propofol 2.5 µg ml^{-1} and greater (fig. 1).

The Intralipid concentrations used during this study were 16.6 µg ml^{-1}, 25 µg ml^{-1}, 33.3 µg ml^{-1} and 333.3 µg ml^{-1}. Random locomotion was reduced also with Intralipid. The degree of reduction was similar to that with Diprivan and propofol. However, Intralipid did not reduce the migration when FMLP was used as chemoattractant (fig. 1). Directional locomotion towards C5a was reduced with Intralipid in concentrations greater than 33.3 µg ml^{-1}, to a similar degree as that with Diprivan (fig. 1).

COMMENT

The major findings of this study were that clinically relevant concentrations of Diprivan depressed migration of the human neutrophil granulocyte. As the reduction was comparable with Diprivan, propofol and Intralipid for random migration and directed migration towards C5a, we conclude that both the drug propofol *per se* and the emulsifier with a composition similar to that of Intralipid were responsible for the influence on the granulocytes. These effects were neither additive nor concentration-dependent. The depressed migration ability of granulocytes after Intralipid incubation in our study was comparable to the results obtained in a previous study [1] in which an *E. coli* culture filtrate was used as chemotactic agent. With the design of our study we were not able to determine whether or not the impairment was reversible after discontinuation of the anaesthetic, and the clinical significance of this inhibition has not yet been determined. However, any impairment of the responsiveness of the leucocyte is likely to increase the incidence of infection. The Leucocyte Adhesion Deficiency, in which defects in neutrophil chemotaxis and phagocytosis lead to widespread bacterial infections, is an example of such an impairment [4].

Leucocytes have been shown to engulf Intralipid, resulting in reduction in important cell membrane constituents and impaired locomotion [1]. The mechanism by which propofol interferes with the locomotor process is not known but, as propofol is lipid soluble, the depressing effect of this agent on random locomotion could also be mediated by membrane changes induced by the drug. Also, the compounds used in this study could possibly exert their effect on migration by disruption of the contractile system.

Specific receptors for C5a and for FMLP on the surface of neutrophils have been demonstrated, and their recycling patterns are different, as are the basic mechanisms for recognition of chemotactic gradients [5]. This could possibly explain the different results found using these two chemoattractants. The turnover of receptors, and the ability to detect a surface bound gradient, may be disturbed by lipid soluble molecules that can be inserted into lipid membranes. The degree of depression of chemotactic locomotion observed with inhalation anaesthetic agents parallels their lipid solubilities [6] and we suggest that propofol could depress locomotion of leucocytes by the same mechanisms as the inhalation anaesthetics.

ACKNOWLEDGEMENT

The authors thank ICI for supplying propofol.

REFERENCES

1. Wiernik A, Jarstrand C, Julander I. The effect of Intralipid on mononuclear and polymorphonuclear phagocytes. *American Journal of Clinical Nutrition* 1983; 37: 256–261.
2. Dahlgren C, Magnusson K-E, Sundqvist T. Concentration gradients in the under-agarose chemotaxis assay system with attractant surface adsorption. *Journal of Immunology Methods* 1984; 75: 23–29.
3. Zigmond SH, Hirsch JG. Leukocyte locomotion and chemotaxis, new methods for evaluation, and demonstration of a cell-derived chemotactic factor. *Journal of Experimental Medicine* 1973; 137: 387–410.
4. Anderson DC. Leucocyte Adhesion Deficiency: An inherited defect in the Mac-1, LFA-1, and p 150,95 glycoproteins. *Annual Review of Medicine* 1987; 38: 175–194.
5. Schiffman E, Gallin JI. Biochemistry of phagocyte chemotaxis. *Current Topics in Cell Regulation* 1979; 15: 203–261.
6. Moudgil GC, Gordon J, Forrest JB. Comparative effects of volatile anaesthetic agents and nitrous oxide on human leucocyte chemotaxis *in vitro*. *Canadian Journal of Anaesthesia* 1984; 31: 631–637.

British Journal of Anaesthesia 1993; 70: 101–103

CASE REPORTS

USE OF TRANSOESOPHAGEAL ECHOCARDIOGRAPHY TO MANAGE BETA-ADRENOCEPTOR BLOCK AND ASSESS LEFT VENTRICULAR FUNCTION IN A PATIENT WITH PHAEOCHROMOCYTOMA

T. RYAN, A. TIMONEY AND A. J. CUNNINGHAM

SUMMARY

A case of phaeochromocytoma is reported in which perioperative hypertension was controlled with an infusion of esmolol. Transoesophageal echocardiography was used in addition to conventional monitoring to manage i.v. fluid administration and assess perioperative changes in left ventricular function. (Br. J. Anaesth. 1993; **70**: 101–103)

KEY WORDS

Monitoring: echocardiography. Pharmacology: esmolol. Surgery: phaeochromocytoma.

Phaeochromocytoma is a catecholamine-secreting tumour which arises usually from the adrenal medulla. This rare tumour may be associated with significant perioperative morbidity and mortality [1, 2]. Esmolol, an ultra-short-acting beta-adrenoceptor blocking agent, may be used to control intraoperative hypertension and tachycardia. This report describes a case in which transoesophageal echocardiography was used to assist intraoperative fluid management and to assess left ventricular function when esmolol infusion was administered during resection of a phaeochromocytoma.

CASE REPORT

A 25-yr-old, 50-kg female presented with an 8-month history of hypertension and tachyarrhythmias. The 24-h urinary concentrations of noradrenaline 1630 µg (normal < 100 µg) and adrenaline 54 µg (normal < 20 µg) were increased. Computed axial tomography demonstrated bilateral adrenal masses consistent with a diagnosis of phaeochromocytoma. Preoperative preparation included alpha-adrenoceptor block with phenoxybenzamine 20 mg orally 8-hourly and propranolol 10 mg orally 6-hourly for 10 days before surgery. There was no evidence of cardiac failure on physical examination or chest radiography. Electrocardiography revealed left ventricular hypertrophy without ST- or T-wave abnormalities. Ambulatory arterial pressure monitoring for 24 h before surgery revealed systolic pressures in the range 100–180 mm Hg and diastolic pressures of 60–90 mm Hg.

Diazepam 10 mg was administered orally 60 min before surgery. Monitoring before induction of anaesthesia consisted of an ECG in the cm5 configuration, direct measurement of arterial pressure and pulse oximetry. Anaesthesia was induced with fentanyl 400 µg and thiopentone 250 mg, followed by vecuronium 10 mg. The lungs were ventilated by mask with 2% isoflurane in oxygen until muscle relaxation was adequate to permit attempts at laryngoscopy and tracheal intubation. Esmolol 0.5 mg kg^{-1} and lignocaine 1.5 mg kg^{-1} were administered to attenuate adverse haemodynamic responses to laryngoscopy and intubation. Anaesthesia was maintained with 0.5–1.0% isoflurane and 50% nitrous oxide in oxygen. A thermodilution pulmonary artery catheter was inserted via the right internal jugular vein and a 5-MHz transoesophageal echocardiac probe (Hewlett–Packard 77020) was inserted to view the short axis of the left ventricle at mid papillary muscle level. This view allows left ventricular cross sectional area to be measured at end-systole (LVESA) and end-diastole (LVEDA) by the following method. Transgastric images of the left ventricular short axis at mid papillary muscle level, gated by an ECG, are recorded on video tape. On replay of individual frames, the left ventricular cavity may be outlined by a light pen. Software incorporated in the ultrasound machine measures the areas outlined. LVEDA is defined as that area which coincides with the peak of the R wave of an ECG; LVESA is taken as the smallest left ventricular cross sectional area. Measurements from three consecutive sinus beats were averaged to arrive at each value of LVEDA and LVESA. Area ejection fraction (AEF) may be derived from LVEDA and LVESA:

$$\text{AEF} = (\text{LVEDA} - \text{LVESA})/\text{LVEDA}$$

Baseline measurements of cardiac index (CI), pulmonary artery occlusion pressure (PAOP), arterial pressure (AP), LVESA, LVEDA and AEF were recorded after tracheal intubation and before surgical incision. M-mode echocardiac measurement of end-diastolic left ventricular free wall thickness, at 1.9 cm, was diagnostic of left ventricular hypertro-

---

T. Ryan*, F.F.A.R.C.S.I.; A. Timoney, M.B.; A. J. Cunningham, F.R.C.P.C.; Department of Anaesthesia, Beaumont Hospital, Beaumont, Dublin, Ireland. Accepted for Publication: July 17, 1992.

*Present address, for correspondence: Department of Anaesthesia, University of Washington, Seattle 98195, U.S.A.

TABLE I. *Perioperative haemodynamic and echocardiographic variables. HR = Heart rate; AP = systemic arterial pressure; CI = cardiac index; SV = stroke volume; PAOP = pulmonary artery occlusion pressure; EDA = end-diastolic area; ESA = end-systolic area; AEF = area ejection fraction. Events: 1 = baseline; 2 = volume loading; 3–7 = surgery; 5 = tumour manipulation; 8 = after surgery*

	Event No.							
	1	2	3	4	5	6	7	8
HR (beat min^{-1})	76	85	74	67	87	78	57	78
AP (mm Hg)	122/70	100/56	105/66	105/67	164/95	106/62	116/69	129/68
CI (litre min^{-1} m^{-2})	4.3	6.6	3.7	3.9	5.0	3.6	3.1	4.6
SV (ml)	85	120	104	88	86	70	82	90
PAOP (mm Hg)	7	12	14	14	16	12	21	13
EDA (cm^2)	9.1	13.6	14.0	13.9	15.9	13.7	14.1	13.2
ESA (cm^2)	4.9	6.6	8.4	9.7	7.9	8.1	8.6	5.3
AEF (%)	48	51	41	30	51	41	40	62
Esmolol (mg kg^{-1} h^{-1})	0	0	0.1	0.1	0.1	0.1	0.1	0

phy. Two-dimensional echocardiography demonstrated a small but vigorously contracting left ventricle.

Colloid solution 1.5 litre was infused rapidly. This was associated with an increase in PAOP from 7 to 12 mm Hg and LVEDA from 9.1 to 13.6 cm^2. Simultaneous increases in AEF (from 48 to 51%) and stroke volume (from 85 to 120 ml) were recorded. Table I details the haemodynamic and echocardiographic data collected during the surgical procedure. An infusion of esmolol 0.1 mg kg^{-1} was commenced in response to hypertension at skin incision, resulting in an increase in LVESA with reduced AEF and stroke volume (table I). Esmolol infusion reduced AEF to a minimum of 30%, with an associated maximum LVESA of 9.7 cm^2. LVEDA was used to assess requirement for i.v. fluid administration. An additional 2 litre of crystalloid solution was necessary to maintain LVEDA in the range 13–16 cm^2. Simultaneous measurements of PAOP at each assessment of LVEDA (table I) varied from 12 to 21 mm Hg. Catecholamine release at tumour manipulation (table I) caused transient hypertension and increase in heart rate, with little change in stroke volume or ejection fraction. Arterial pressure was unchanged after ligation of the venous drainage of the tumour. At termination of surgery, when esmolol infusion was discontinued, LVESA decreased, with associated increase in arterial pressure, AEF and cardiac index (table I). As the estimated intraoperative blood loss was 500 ml, homologous blood was not transfused. The patient's postoperative recovery was uneventful. Histology confirmed the presence of bilateral phaeochromocytoma.

DISCUSSION

The traditional management of hypertension and tachycardia associated with phaeochromocytoma excision combines preoperative preparation with alpha-adrenoceptor block and intraoperative use of potent vasodilators such as nitroprusside [1]. Hypertensive episodes caused by surges in plasma catecholamine concentrations may be observed at tracheal intubation, skin incision and tumour manipulation. Hypotension may occur after ligation of the venous drainage of the tumour and is mainly a result of hypovolaemia [2].

Two-dimensional echocardiography may be used to assess left ventricular function by calculating area ejection fraction from end-diastolic and end-systolic left ventricular areas. Transoesophageal echocardiography (TE) may be used to provide a reliable and reproducible index of peroperative left ventricular end-diastolic volume and ejection fraction. Abel and colleagues found the median intra-observer variability in measurement of AEF to be 3%, with a 75th percentile of 5.75% [3]. Smith and colleagues showed that deliberate repositioning of a TE probe does not result in significant change in measured values of LVEDA and LVESA [4]. Additionally, LVEDA and AEF on TE correlate significantly with radionuclide measurement of end-diastolic volume and ejection fraction [5].

Ejection fraction is dependent on both preload and afterload and thus is an imprecise index of left ventricular function. However, LVESA is related linearly to systemic arterial pressure [6]. With constant arterial pressure, deteriorating contractility should be accompanied by increased LVESA on TE. This relationship between systemic arterial pressure and LVESA may be used to assess contractility. In a report on echocardiographic findings associated with phaeochromocytoma, Shub and colleagues [7] documented normal systolic function in 23 of 26 patients. In this patient, before surgical incision and esmolol infusion, TE left ventricular short axis imaging demonstrated normal systolic function. Esmolol reduces left ventricular contractility and the infusion of esmolol induced a marked reduction in ejection fraction during surgery. This was reversed temporarily, on tumour manipulation, presumably because of an increase in catecholamine concentrations. LVESA was increased by infusion of esmolol, despite near constant systemic arterial pressure. LVESA and AEF returned to baseline values shortly after esmolol was discontinued. These echocardiographic measurements, AEF and LVESA, served as an index of myocardial function against which esmolol infusion may be titrated.

Pulmonary artery occlusion pressure represents an estimate of left ventricular end-diastolic pressure and, in comparison with TE-derived LVEDA, is an imprecise index of left ventricular end-diastolic volume [5]. In the presence of impaired left ventricular compliance, secondary to left ventricular hypertrophy, hypovolaemia may occur when PAOP lies within the normal range. Intraoperative M-mode TE was used in our patient to confirm a preoperative diagnosis of left ventricular hypertrophy. Left ventricular free wall thickness was 1.9 cm, compared with normal limits of 1–1.2 cm [8]. Hypovolaemia is an important contributing factor to the profound hypotension that may occur after removal of a phaeochromocytoma [1]. In this patient, TE two-dimensional echocardiographic measurement of LVEDA was used to monitor left ventricular preload. I.v. fluids were titrated to maintain LVEDA on TE at the value attained after initial infusion of i.v. fluids. PAOP varied from 12 to 21 mm Hg during surgery, despite minimal changes in LVEDA on TE (13.6–15.9 cm^2). In this manner, occult hypovolaemia was avoided and hypotension after tumour removal was prevented.

Although preoperative medication with alpha-adrenoceptor blocking drugs remains a cornerstone of management, the role of newer beta-adrenoceptor blockers such as esmolol has not been fully evaluated. The use of beta-adrenergic block has been limited by two major concerns. First, in the presence of a catecholamine-induced cardiomyopathy, these negative inotropic agents might precipitate cardiac failure. Second, peripheral beta-adrenoceptor block may oppose peripheral vasodilatation and augment pre-existing hypertension [1, 2]. Esmolol is a short-acting beta-adrenoceptor blocker which acts within 2 min and has an elimination half-life of 9 min [9]. Thus myocardial dysfunction produced by esmolol is of short duration. As esmolol is also highly cardioselective, it has no peripheral actions [10]. Beta-adrenoceptor block may also be beneficial in preventing perioperative tachyarrhythmias. Esmolol has been used safely as part of the intraoperative management of phaeochromocytoma without either precipitating cardiac failure or aggravating hypertension [11,12]. Thus esmolol should be considered in the prevention and control of hypertension at resection of a phaeochromocytoma when left ventricular systolic function is normal. However, the considerable cost of an esmolol infusion represents a potential disadvantage of this approach.

Vasodilators were not used in the peroperative control of arterial pressure in this patient. Preoperative electrocardiographic evidence of left ventricular hypertrophy was confirmed by intraoperative M-mode echocardiography. Diastolic dysfunction with impaired left ventricular compliance is a consequence of hypertension-induced left ventricular hypertrophy [13]. In the presence of left ventricular hypertrophy, LVEDP should be maintained sufficient to ensure adequate stroke volume and cardiac output. Brush and colleagues [14] utilized nuclear ventriculography and intraventricular pressure monitoring to compare the effects of nitroprusside and verapamil on left ventricular function in hypertensive patients. Nitroprusside, a potent vasodilator, reduced left ventricular end-diastolic pressure. Thus left ventricular end-diastolic volume and cardiac output were reduced by infusion of nitroprusside. In contrast, although verapamil reduced left ventricular contractility, it maintained stroke volume and cardiac output. Brush's group concluded that it is more appropriate to control systemic hypertension with a negative inotropic agent when left ventricular compliance is reduced and ventricular systolic function is normal. Indeed, Topol, Traill and Fortuin [15] suggested that negative inotropic agents are the hypotensive agents of choice in patients with left ventricular hypertrophy. In the patient reported here, phaeochromocytoma was associated with left ventricular hypertrophy and preserved left ventricular systolic function. Vasodilating hypotensive agents may be contraindicated in this patient.

REFERENCES

1. Desmonts JM, Marty J. Anaesthetic management of patients with phaeochromocytoma. *British Journal of Anaesthesia* 1984; **56**: 781–789.
2. Pullerits J, Ein S, Balfe JW. Anaesthesia for phaeochromocytoma. *Canadian Journal of Anaesthesia* 1988; **35**: 526–534.
3. Abel MD, Nishimura RA, Callahan MJ, Rehder K, Ilstrup DM, Tajik JA. Evaluation of intraoperative transesophageal two dimensional echocardiography. *Anesthesiology* 1987; **66**: 64–68.
4. Smith JS, Cahalan MK, Benefiel DJ, Byrd BF, Lurz FW, Shapiro WA, Roizen MF, Bouchard A, Schiller NB. Intraoperative detection of myocardial ischaemia in high risk patients: electrocardiography versus two dimensional transesophageal echocardiography. *Circulation* 1985; 72: 1015–1021.
5. Clemens FM, Harpole DH, Quill T, Jones RH, McCann RH. Estimation of left ventricular volume and ejection fraction by two-dimensional transoesophageal echocardiography. Comparison of short axis imaging and simultaneous radionuclide angiography. *British Journal of Anaesthesia* 1990; **64**: 331–336.
6. Heinrich H, Fosel T, Fontaine L, Spilker D, Winter H, Ahnefeld FW. Assessment of contractility changes in humans by transoesophageal echocardiography: The peak systolic pressure end-systolic diameter relationship (PSPESDRS). *International Journal of Clinical Monitoring and Computing* 1987; 4: 243–248.
7. Shub C, Cueto-Garcia L, Sheps SG, Ilstrup DM, Tajik J. Echocardiographic findings in pheochromocytoma. *American Journal of Cardiology* 1986; **57**: 971–975.
8. Feigenbaum H. *Echocardiography*. Philadelphia: Lea & Febiger, 1986; 628.
9. Gorczynski RJ. Basic pharmacology of esmolol. *American Journal of Cardiology* 1985; **56**: 3–13F.
10. Gorczynski RJ, Murthy VS, Hwang TF. Beta blocking and hemodynamic effects of ASL 8052. *Journal of Cardiovascular Pharmacology* 1984; **6**: 1048–1059.
11. Zakowski M, Kaufman B, Berguson P, Tissot M, Yarmush L, Turndorf H. Esmolol use during resection of pheochromocytoma. *Anesthesiology* 1989; **70**: 875–877.
12. Nicholas E, Deutschman CS, Allo M, Rock P. Use of esmolol in the intraoperative management of pheochromocytoma. *Anesthesia and Analgesia* 1988; **67**: 1114–1117.
13. Shub C. Heart failure and abnormal ventricular function. *Chest* 1989; **96**: 906–914.
14. Brush JE, Udelson JE, Bacharach SL, Cannon RO, Leon MB, Rumble TF, Bonow RO. Comparative effects of verapamil and nitroprusside on left ventricular function in patients with hypertension. *Journal of the American College of Cardiology* 1989; **14**: 515–522.
15. Topol EJ, Traill TA, Fortuin NJ. Hypertensive hypertrophic cardiomyopathy of the elderly. *New England Journal of Medicine* 1985; **312**: 277–283.

British Journal of Anaesthesia 1993; 70: 104–106

USE OF ESMOLOL IN THE POSTBYPASS MANAGEMENT OF HYPERTROPHIC OBSTRUCTIVE CARDIOMYOPATHY

L. G. OOI, P. J. O'SHEA AND A. J. WOOD

SUMMARY

In patients suffering from hypertrophic obstructive cardiomyopathy (HOCM), any catecholamine release during anaesthesia may aggravate the severity of the outflow tract obstruction and compromise cardiac output. In this event the situation may be improved by beta block. Esmolol, an ultra-short-acting beta-blocker (half-life 9 min) appears to be a suitable agent for this purpose. We describe its use in the perioperative management of a patient who underwent surgical correction of HOCM. (Br. J. Anaesth. 1993; **70**: 104–106)

KEY WORDS

Complications: hypertrophic obstructive cardiomyopathy. Sympathetic nervous system: β-adrenoceptor block, esmolol.

Hypertrophic obstructive cardiomyopathy (HOCM) is transmitted genetically as an autosomal dominant with a high degree of penetrance [1–3]. The anatomical abnormality is asymmetrical hypertrophy of the interventricular septum, with bizarrely shaped and disorganized cardiac muscle fibres. This is believed to be caused by an increased density of voltage-sensitive calcium channels which impair normal muscular relaxation [2]. The result is an outflow tract obstruction between the left ventricle and the aortic valve, with accompanying left ventricular hypertrophy and poor left ventricular compliance. The obstruction is made worse during systole by exaggerated movement of the anterior mitral valve leaflet towards the septum, the so-called systolic anterior motion (SAM) [3]. Clinical manifestations of the disease include angina, dyspnoea, palpitations and syncope. There is also an increased incidence of sudden death attributable to ventricular arrhythmias.

Surgical correction of HOCM, by either septal myotomy or partial myomectomy, is usually reserved for patients with severe symptoms despite optimal drug therapy or with evidence of a large outflow tract gradient [4]. The main anaesthetic consideration is to prevent or minimize any factor that would increase the outflow tract gradient perioperatively. We present the case report of a patient who underwent surgical correction of HOCM. During the immediate post-cardiopulmonary bypass period and after operation, in the intensive care unit, we used esmolol, with improvement in the outflow tract gradient.

CASE REPORT

A 54-yr-old lady presented to the cardiology clinic with a 6-month history of increasing central chest pain on exertion. She had no previous medical history. On examination, she had a resting arterial pressure of 130/80 and her heart rate was 72 beat min^{-1}, regular. An early systolic murmur was detected at the apex, radiating into the aortic area. Her exercise test was positive, with ST segment changes greater than 2 mm in leads V5 and V6. An echocardiogram was performed which showed a hypertrophied left ventricle. Subsequent cardiac catheterization revealed a gradient of 84 mm Hg between the left ventricle and the outflow tract, and a gradient of 21 mm Hg between the outflow tract and the aorta. The coronary arteries were normal and the patient was scheduled to undergo myomectomy of the left ventricular outflow tract 2 weeks later.

On the day of the operation, she was premedicated with diazepam 10 mg 2 h before operation and papaveretum 15 mg and hyoscine 0.3 mg 1 h before operation. Before induction, a peripheral i.v. cannula was inserted and direct arterial pressure monitoring commenced via a 20-gauge cannula in the left radial artery. Anaesthesia was induced with fentanyl 250 μg, thiopentone 150 mg and pancuronium 12 mg. After tracheal intubation, intermittent positive pressure ventilation was commenced and anaesthesia maintained with nitrous oxide and enflurane in oxygen, and incremental doses of fentanyl as clinically indicated. A central venous cannula and a pulmonary artery thermodilution catheter were inserted via the right internal jugular vein.

Baseline haemodynamic readings before surgical incision are shown in table I. Sternotomy produced an increase in arterial pressure to 150/90 mm Hg which was controlled by a further incremental dose of fentanyl 250 μg. Thereafter, all the cardiovascular parameters remained stable until cardiopulmonary bypass (CPB) was commenced.

During CPB, the patient was cooled to 28 °C, the aorta was crossclamped and cardioplegia solution 700 ml infused. The aortic valve was exposed and

---

L. G. Ooi, M.B., CH.B., F.R.C.ANAES., P. J. O'Shea, M.B., B.S., F.R.C.ANAES. (Department of Anaesthesia); A. J. Wood, F.R.C.S. (Department of Cardiothoracic Surgery); The Royal London Hospital, Whitechapel, London E1 1BB. Accepted for Publication: July 28, 1992.

TABLE I. *Haemodynamic data before and after cardiopulmonary bypass*

	Heart rate (beat min^{-1})	AP (mm Hg)	CVP (mm Hg)	PCWP (mm Hg)	LV outflow tract gradient (mm Hg)
Immediately before CPB	80	130/80	6	9	84
Immediately after CPB	100	80/60	6	10	50
15 min after esmolol	75	130/80	8	13	10
15 min after end esmolol	85	100/60	8	12	25
15 min after esmolol restart	80	125/70	8	12	10

found to be normal, and hypertrophic muscle was seen in the outflow tract through the aortic valve. Myomectomy was performed on the left ventricular outflow tract. Immediately after discontinuation of CPB, arterial pressure was 80/60 mm Hg. The filling pressure was increased to a PCWP of 12 mm Hg with colloid and trial use of the vasoconstrictor metaraminol failed to produce any improvement in arterial pressure. Measurement of the pressures within the left ventricle and the left ventricular outflow tract revealed a gradient of 50 mm Hg. CPB was recommenced and esmolol 3 mg kg^{-1} h^{-1} infused after a loading dose of 500 μg kg^{-1} given over 1 min. Fifteen minutes later, CPB was again discontinued. Cardiovascular variables improved significantly and the left ventricular outflow tract gradient was now 10 mm Hg. The patient remained haemodynamically stable for 30 min, whereupon the esmolol was discontinued. Within 15 min, however, the left ventricular outflow tract gradient had increased to 25 mm Hg. The esmolol infusion was recommenced and the haemodynamic state improved.

The patient remained haemodynamically stable thereafter and after completion of surgery she was transferred to the intensive care unit. The esmolol infusion was continued for another 12 h at a rate of 2 mg kg^{-1} h^{-1}; filling pressures were maintained at optimal values and she remained stable. The following morning the trachea was extubated and the esmolol infusion was discontinued when oral propanolol had been instituted.

DISCUSSION

One of the features of HOCM is the dynamic nature of the outflow tract obstruction. The degree and timing of SAM-septal contact of the anterior mitral valve leaflet determines the dynamic pressure gradient [3] and it is influenced by myocardial contractility, preload and afterload. Hypovolaemia, peripheral vasodilatation and increased sympathetic tone increase the pressure gradient while, paradoxically, factors which usually impair left ventricular performance, such as myocardial depression, systemic vasoconstriction and ventricular overdistension, reduce outflow tract obstruction.

Any hypotension during operation should be treated initially by optimizing left ventricular filling pressures using PCWP measurements as a guide to intravascular filling; the CVP is less likely to reflect changes in left ventricular volume. Where necessary, systemic vascular resistance is maintained by the use of peripheral vasoconstrictors. Inotropic agents increase left ventricular contractility and therefore may provoke additional obstruction by increasing the contractility of the abnormal muscle in the outflow tract. Beta blockers, in contrast, by suppressing sympathetic stimulation, decrease the pressure gradient and improve cardiac output. Their use in the medical management of HOCM is well-documented [3]. Esmolol is a relatively new cardiac selective beta blocker with a short half-life (9 min) when administered i.v. [5]. It has already been used in a number of situations in which beta block of limited duration is required—for example, attenuation of the sympathetic response to laryngoscopy and tracheal intubation [6], treatment of superventricular tachycardia [5] and intraoperative management of phaeochromocytoma [7]. In our patient, we found that an infusion of esmolol produced a decrease in heart rate, a significant decrease in the outflow tract gradient and an improvement in arterial pressure. Its duration of action is relatively short; the effects disappeared within 15 min of discontinuation of the infusion.

It is interesting to note the changes in the left ventricular outflow tract gradient. Before CPB, the gradient was 84 mm Hg, but after CPB it had decreased to 50 mm Hg, suggesting that surgical myomectomy had made some improvement but the patient was not sufficiently stable. Surgical opinion was that further myomectomy could weaken the septal wall, with the probability of causing a ventricular septal defect. Metaraminol was tried, but did not improve the situation. Esmolol was therefore tried because of its short half-life. After the esmolol infusion was started, the ventricular outflow tract gradient had decreased to 10 mm Hg. It was therefore decided to stop the esmolol to see if the drug had made any improvement to the gradient. After cessation of esmolol infusion, the gradient increased to 25 mm Hg and it was only after recommencing the drug that the gradient was again reduced.

REFERENCES

1. Bridgen W. Hypertrophic cardiomyopathy. *British Heart Journal* 1987; 58: 299–302.
2. Braunwald E. Hypertrophic cardiomyopathy—continued progress. *New England Journal of Medicine* 1989; 320: 749–755.

3. Jackson JM, Thomas SJ. Valvular heart disease. In: Kaplan JA, ed. *Cardiac Anaesthesia*, Vol. 2. London: Grune and Stratton, Inc., 1987; 602–609.
4. Mohr R, Schaff HV, Danielson GK, Puga FJ, James RP, Tajik AJ. The outcome of surgical treatment of hypertrophic obstructive cardiomyopathy. *Journal of Thoracic and Cardiovascular Surgery* 1989; **97**: 666–674.
5. Ramsay JG. Esmolol. *Canadian Journal of Anaesthesia* 1991; **38**: 155–158.
6. Menkhaus PG, Reves JG, Kissin I, Alvis JM, Govier AV, Samuelson PN, Lell WA, Henling CE, Bradley E. Cardiovascular effects of esmolol in anesthetized humans. *Anesthesia and Analgesia* 1985; **64**: 327–334.
7. Zakowski M, Kaufman B, Berguson P, Tissot M, Yarmish L, Turndoff H. Esmolol use during resection of pheochromocytoma: Report of three cases. *Anesthesiology* 1989; **70**: 875–877.

British Journal of Anaesthesia 1993; **70**: 107–109

PROLONGED USE OF ISOFLURANE IN A PATIENT WITH TETANUS

J. J. W. M. STEVENS, R. M. GRIFFIN AND P. J. STOW

SUMMARY

We describe a patient with tetanus, who received isoflurane for sedation to facilitate controlled mechanical ventilation. Isoflurane was administered for 34 days, resulting in a sustained serum inorganic fluoride ion concentration in excess of 50 μmol litre^{-1} and a peak serum inorganic fluoride ion concentration of 87 μmol litre^{-1}. Although these concentrations are potentially nephrotoxic, no toxicity was evident clinically. (Br. J. Anaesth. 1993; **70**: 107–109)

KEY WORDS

Anaesthetics, volatile: isoflurane. Infection: tetanus. Kidney: nephrotoxicity.

Tetanus is a condition which requires a period of long-term sedation to facilitate controlled mechanical ventilation. Isoflurane may be a useful agent for long-term sedation because of its minimal metabolism. Furthermore, the effect on the cardiovascular system may be useful to counteract the enhanced autonomic activity associated with tetanus. There are no reports in the anaesthetic literature of the use of isoflurane sedation for tetanus.

CASE REPORT

A 44-yr-old man was admitted for endoscopic surgery to the left maxillary sinus. Before operation he was noted to have difficulty in swallowing and he complained of tightening of the face and neck muscles. Surgery was cancelled and over the following 5 days he developed muscle spasm in the abdomen and legs. A diagnosis of tetanus was made; exposure to the tetanus bacillus had probably been via soil contact 2 weeks previously. The patient had not received passive tetanus immunization because of an allergic reaction to the toxoid in childhood. In his previous medical history he was known to be allergic to penicillin and non-steroidal anti-inflammatory drugs. He was an asthmatic treated with phyllocontin, becotide and salbutamol, but had never received oral steroid treatment.

The patient was transferred to the Intensive Therapy Unit and treated initially with i.v. diazepam in emulsion. In the course of the next 24 h he developed progressive difficulty with swallowing and he required elective tracheal intubation and controlled mechanical ventilation. He was sedated with continuous infusions of propofol 80 mg h^{-1}, fentanyl 70 μg h^{-1} and midazolam 5 mg h^{-1}, with atracurium 30 mg h^{-1} for neuromuscular block.

Tracheotomy was performed on day 5 to facilitate long-term ventilation. By day 21 of ventilation, requirements for propofol and fentanyl had increased to 230 mg h^{-1} and 180 μg h^{-1}, respectively. The dose of atracurium to provide adequate muscle paralysis, as assessed by peripheral nerve stimulation (Bard critical care Model 750), had increased to 100 mg h^{-1}. During this period, sedation remained inadequate by clinical assessment (modified Ramsey scale 1–2), and there was intermittent marked variability in arterial pressure and heart rate. Isoflurane was administered in an attempt to achieve better sedation and improve cardiovascular stability, using a Siemens vaporizer Model 952 and charcoal canisters for scavenging. Propofol and midazolam infusions were stopped and sedation maintained for an additional 34 days with a mean infusion of fentanyl 140 μg h^{-1} (range 100–160 μg h^{-1}) and expired isoflurane concentration of 0.8–1.2% measured with a Kontron anaesthetic agent monitor 7860. This concentration was necessary to provide adequate sedation. Isoflurane administration was stopped for a period of 48 h between days 32 and 34 of ventilation because of a shortage of charcoal cannisters. Vecuronium was substituted for atracurium on day 32 with a mean dose of 4 mg h^{-1} (range 3–7 mg h^{-1}).

Urine output was monitored hourly, serum creatinine and urea concentrations measured daily and liver function tests measured twice weekly (table I). Serum fluoride concentrations (fig. 1) were measured with a selective fluoride ion electrode (Orion, model 94-09).

On day 41, sedation was stopped to assess the need for controlled ventilation. The patient was responsive within 30 min but he subsequently developed muscle spasm requiring resedation, muscle relaxation and further ventilation. On day 57 another attempt at weaning was made. The patient regained consciousness after 1 h and after 2 h was alert, orientated and able to repeat his date of birth. However, he remained in a withdrawn state, and after 48 h, exhibited several episodes of uncoordinated muscle spasm, possibly of a convulsive nature. Although electroencephalography was not undertaken, the spasms were treated empirically

---

J. J. W. M. STEVENS, D.A.; R. M. GRIFFIN, F.R.C.ANAES.; P. J. STOW, F.R.C.ANAES.; The Ipswich Hospital, Heath Road, Ipswich IP4 5PD. Accepted for Publication: August 14, 1992.

TABLE I. *Renal and hepatic indices with prolonged isoflurane anaesthesia*

Day:	1	10	17	29	31	33	35	38
Urine out (ml h^{-1})	2920	2345	3162	1370	2255	1825	1892	1544
Urea (mmol litre^{-1})	2.1	4.6	6.0	5.2	5.1	7.7	7.3	7.4
Creatinine (µmol litre^{-1})	106	71	60	60	59	59	52	50
Protein (g litre^{-1})	64	58	60	60	61	56	66	62
Albumin (g litre^{-1})	45	35	33	32	33	32	37	34
Globulin (g litre^{-1})	19	33	27	28	28	24	29	28
ALT (u. litre^{-1})	18	92	143	153	160	129	155	235
ALP (u. litre^{-1})	181	251	1008	1125	1029	831	849	834
Total bilirubin (µmol litre^{-1})	18	5	15	5	6	6	11	10

Day:	40	42	45	48	53	60	63	67
Urine out (ml h^{-1})	1585	1882	2420	1613	1190	1408	2285	1700
Urea (mmol litre^{-1})	8.4	4.7	5.3	9.0	6.0	5.7	5.7	5.4
Creatinine (µmol litre^{-1})	50	54	48	57	52	48	48	56
Protein (g litre^{-1})	62	60	58	61	65	62	65	61
Albumin (g litre^{-1})	32	32	32	34	37	34	37	37
Globulin (g litre^{-1})	30	26	26	27	28	28	28	24
ALT (u. litre^{-1})	218	99	102	122	178	134	86	63
ALP (u. litre^{-1})	847	648	668	669	686	519	483	412
Total bilirubin (µmol litre^{-1})	10	11	6	5	6	3	6	10

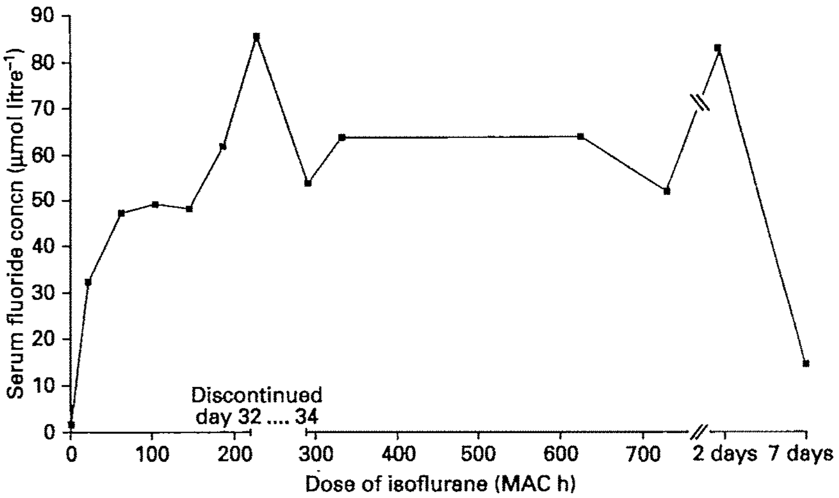


FIG. 1. Serum fluoride concentrations as a function of dose of isoflurane. The last two samples were taken after discontinuation for 2 and 7 days.

with phenytoin. The patient experienced hallucinations for a period of 5 days, but these gradually resolved. His subsequent recovery was uneventful and he was discharged from hospital 6 weeks after leaving the ITU.

DISCUSSION

Sedation, neuromuscular block and controlled ventilation are required for the treatment of severe tetanus. Tetanus may be complicated by sympathetic nervous system overactivity, with tachycardia, labile hypertension, peripheral vasoconstriction and myocardial irritability [1]. Isoflurane reduces hypertension by decreasing peripheral vascular resistance, and suppresses catecholamine release more effectively than midazolam [2]. Therefore, it seemed appropriate to sedate this patient, a known asthmatic, with isoflurane, as large doses of propofol, midazolam and fentanyl had proven inadequate. Although the quality of sedation (modified Ramsey scale 3) was improved, there was no marked improvement in cardiovascular stability after the introduction of isoflurane even though we thought that the variability in arterial pressure was caused by inadequate sedation rather than autonomic dysfunction.

We chose atracurium initially for neuromuscular paralysis because of its complete metabolism and lack of accumulation, and it has been shown previously to be useful for the management of tetanus [3]. However, after the development of a moderate degree of bronchospasm, vecuronium was substituted. Respiratory function improved, and a greater degree of haemodynamic stability was observed, in accordance with observations in a previous report of a patient with tetanus [4].

Isoflurane was administered in a greater concentration than reported previously because of patient requirement. Unfortunately, results of fluoride ion assay were not available until after discharge of the patient from the ITU. However, the serum concentration of fluoride increased during the first 72 h, as reported in a short term study of isoflurane [5]. A recent longer term study (up to

30 MAC h) showed also a continuous increase in plasma concentrations of fluoride [6]. In our patient, the plasma concentration of fluoride reached a plateau at 50 MAC h; however, only two samples were available between 300 and 700 MAC h. The serum concentration of fluoride increased again when isoflurane was discontinued. Both peaks of 87 and 83 μmol litre^{-1} occurred after isoflurane had been discontinued for 48 h (fig. 1). Metabolism of isoflurane begins with oxidation of the carbon–halogen link of the alpha carbon, leading to difluoromethanol and trifluoroacetic acid. Trifluoroacetic acid is resistant to oxidative and reductive breakdown, but difluoromethanol is metabolized to formic acid with release of two fluoride ions. In a previous study, enflurane metabolism was inhibited by administration of isoflurane [7]. Therefore, it is possible that isoflurane inhibits its own metabolism or that there are significant interindividual variations in metabolism of isoflurane.

Animal [8] and clinical [9] studies have investigated the toxicity of fluoride accumulation during methoxyflurane anaesthesia. In man, at serum fluoride concentrations greater than 50 μmol litre^{-1}, subclinical toxicity occurred, with increased serum uric acid concentration. A serum fluoride concentration exceeding 90 μmol litre^{-1} is associated with a variable degree of toxicity manifest by serum hyperosmolality, hypernatraemia, polyuria and low urine osmolality. Despite prolonged exposure to a fluoride ion concentration greater than 50 μmol litre^{-1}, our patient showed no increase in urinary volume or increase in serum creatinine and urea concentration, which might have been indicative of nephrotoxicity. This is in agreement with other reports of prolonged administration of isoflurane [6, 10].

The muscle spasm resembling convulsive activity after withdrawal of sedation is difficult to explain. Isoflurane does not have proconvulsant properties [11], and long term infusion of atracurium in a patient with tetanus has not been shown to cause excessive accumulation of laudanosine [3]. It is possible that the observed phenomenon represented residual muscle spasm, as has been described previously in tetanus [12]. Dantrolene 1–2 mg kg^{-1} has been used as a spasmolytic agent in mild and moderate tetanus, but experience is limited in severe tetanus and its use was considered inappropriate for this patient.

This case report demonstrates that prolonged administration of isoflurane is associated with potentially toxic concentrations of serum inorganic fluoride, although no clinical effect on renal function was found. This paradoxical finding indicates that further investigation into the safety of isoflurane in long term use is required before its use can be recommended.

REFERENCES

1. Kerr JH, Corbett JL, Prys-Roberts C, Crampton Smith A. Involvement of the sympathetic nervous system in tetanus. *Lancet* 1968; **2**: 236–241.
2. Kong KL, Willatts SM, Prys-Roberts C, Harvey JT, Gorman S. Plasma catecholamine concentration during sedation in ventilated patients requiring intensive therapy. *Intensive Care Medicine* 1990; **16**: 171–174.
3. Peat SJ, Potter DR, Hunter MJ. The prolonged use of atracurium in a patient with tetanus. *Anaesthesia* 1988; **43**: 962–963.
4. Powells AB, Ganta R. Use of vecuronium in the management of tetanus. *Anaesthesia* 1985; **40**: 879–881.
5. Truog RD, Rice SA. Inorganic fluoride and prolonged isoflurane anesthesia in the intensive care unit. *Anesthesia and Analgesia* 1989; **69**: 843–845.
6. Spencer EM, Willatts SM, Prys-Roberts C. Plasma inorganic fluoride concentrations during and after prolonged isoflurane sedation: effect on renal function. *Anesthesia and Analgesia* 1991; **73**: 731–737.
7. Oikkonen MP. Isoflurane inhibits enflurane metabolism in man. *Anaesthesia* 1989; **44**: 763–764.
8. Mazze RI, Cousins MJ. Dose related methoxyflurane nephrotoxicity in rats. *Anesthesiology* 1972; **36**: 571–587.
9. Cousins MJ, Mazze RI. Methoxyflurane nephrotoxicity. A study of dose response in man. *Journal of the American Medical Association* 1973; **225**: 1611–1616.
10. Breheny FX. Inorganic fluoride in prolonged isoflurane sedation. *Anaesthesia* 1992; **47**: 32–33.
11. Eger EI, Stevens WC, Cromwell TH. The electroencephalogram in man anesthetized with Forane. *Anesthesiology* 1971; **35**: 504–508.
12. Edmondson RS, Flowers MW. Intensive care in tetanus: management complications, and mortality in 100 cases. *British Medical Journal* 1979; **1**: 1401–1404.

British Journal of Anaesthesia 1993; **70**: 110–116

CORRESPONDENCE

POSTOPERATIVE PAIN THRESHOLDS

Sir,—Dahl and colleagues have demonstrated a decrease in the pain threshold and an increase in subjective assessment of pain in postoperative female patients recovering from gynaecological operations [1], in contrast to a lack of alteration in a control group. The degree of hyperalgesia showed a significant inverse correlation with time after surgery. The patients had received morphine and paracetamol after operation, but not for 12 h before testing. Of relevance, however, is the fact that in all patients anaesthesia was induced with thiopentone 4–5 mg kg^{-1} i.v. Thiopentone has long been known to have antanalgesic properties in small doses [2].

Kissin and colleagues have demonstrated that barbiturates inhibit stress-induced analgesia in Sprague–Dawley rats [3]. In this study, a motor reaction threshold to noxious pressure on the tail was measured. Stressing the animal by placing a clamp on the hind paw produced an increase in reaction threshold. Pentobarbitone in subanaesthetic doses largely abolished the stress-induced increase in motor reaction threshold. Stressing the rats on recovery from thiopentone anaesthesia failed to increase the motor reaction threshold from that in the unstressed rat. This parallels the situation in Dahl's study. Wilder-Smith and Borgeat also have demonstrated a hyperalgesic response to small doses of thiopentone in unstressed patients [4]. Their study showed similar results with low-dose propofol, but neither hyperalgesia nor analgesia with etomidate.

In Dahl's study, testing was performed 40–80 h after anaesthesia. At this time, a small proportion of the anaesthetic agent remains within the circulation. This may or may not be sufficient to produce an antanalgesic effect (whether or not the antanalgesic effect is related to plasma concentration is not clear from Kissin's work). The decrease in pain threshold diminishes with time, consistent with a decrease in circulating barbiturate.

The quoted studies do not refute Dahl's findings, but it may be that the increase in postoperative pain perception and decrease in pain threshold are not caused solely by central neuronal sensitization, but that a contribution is made by residual thiopentone. It would be interesting if Dahl's findings were repeated with different anaesthetic induction agents.

T. M. Cook
Royal Cornwall Hospital
Treliske, Truro

1. Dahl JB, Erichsen CJ, Fuglsang-Frederiksen A, Kehlet H. Pain sensation and nociceptive reflex excitability in surgical patients and human volunteers. *British Journal of Anaesthesia* 1992; **69**: 117–121.
2. Dundee JW. Alterations in response to somatic pain associated with anaesthesia II: the effect of thiopentone and pentobarbitone. *British Journal of Anaesthesia* 1960; **32**: 407–414.
3. Kissin I, Mason JO iii, Vinik HR, McDanal J, Bradley EL jr. Barbiturates inhibit stress-induced analgesia. *Canadian Journal of Anaesthesia* 1987; **34**: 146–157.
4. Wilder-Smith O, Borgeat A. Analgesia with subhypnotic dose of thiopentone and propofol. *British Journal of Anaesthesia* 1991; **67**: 226–227.

PHARMACOKINETIC/PHARMACODYNAMIC MODELLING OF ATRACURIUM

Sir,—The multiple elimination pathways of atracurium from both the central and tissue compartments confound its pharmacokinetic/pharmacodynamic analysis and necessitate the use of innovative models. Three recent articles [1–3] proposed models that differ from ours [4]. I contend that each of these new proposed models is flawed.

Beemer, Bjorksten and Crankshaw [1] infused atracurium using a computer-controlled infusion regimen to estimate volume of distribution at steady-state (V^{ss}) as the ratio of the amount of drug in the body at steady-state (X^{ss}) divided by the steady-state atracurium concentration. X^{ss} was estimated as the quantity of atracurium infused minus that eliminated. However, their estimate of the quantity eliminated (the product of plasma clearance and area under the plasma concentration–time curve (0–1 h)) is flawed—it does not account completely for drug eliminated from tissue rather than plasma. Because atracurium is eliminated from both plasma and tissue, Beemer's group underestimated V^{ss}. The authors' retort that they used a non-parametric approach to avoid this problem is invalid—these non-parametric techniques require that elimination be from the central compartment only [5].

Parker and Hunter's interesting approach to relating the recovery of atracurium to its pharmacokinetics used "standard formulae" to estimate V^{ss} [2]. Yet, in their letter to the editor criticizing the manuscript by Beemer, Bjorksten and Crankshaw, they stated that for atracurium, "standard formulae...[do] not allow calculation of the...steady-state volume of distribution as usually defined" [6]. Their letter is correct, their manuscript in error—standard formulae require the assumption, invalid for atracurium, that clearance occurs only in the central compartment. As with Beemer's group, Parker and Hunter underestimate V^{ss}.

Parker and Hunter also propose a new pharmacodynamic model for atracurium in which a threshold concentration is necessary at the neuromuscular junction to produce paralysis [3]. The systematic error they observed fitting the traditional model (leading them to reject that model) may arise from their obtaining venous rather than arterial blood samples—for atracurium (as other drugs), venous concentrations obtained early during an infusion underestimate arterial and effect site concentrations [7]. Alternatively, a more complicated link model may be necessary to explain the relationship between concentrations in the plasma and those at the neuromuscular junction. However, in the absence of actual measurements of effect site concentrations, all pharmacokinetic/pharmacodynamic models describe "black boxes"; therefore, no single model can be demonstrated to be valid or invalid. Parker and Hunter claim that their model provides "explicit demonstration of a margin of safety of neuromuscular transmission in the human". Yet, the margin of safety associated with their model ($C_{threshold} = 159$) differs little from a concentration (120 ng ml^{-1}) that I calculate produces minimal (1%) twitch depression with the traditional model. Perhaps these investigators should evaluate their model using a more appropriate data set (arterial plasma concentrations) before rejecting a well accepted (and parsimonious) model.

Our model for atracurium [4] is the only one to incorporate Dr Hull's editorial suggestion that atracurium's pharmacokinetics can only be determined if the rate of elimination from the peripheral compartment is estimated [8]. Although our model may be flawed, to date no one has presented a cogent argument regarding any errors. I am delighted that this topic has elicited so much interest in the anaesthesia research community, but I believe that errors by these other investigators should be corrected.

D. M. Fisher
University of California
San Francisco, California

1. Beemer GH, Bjorksten AR, Crankshaw DP. Pharmacokinetics of atracurium during continuous infusion. *British Journal of Anaesthesia* 1990; **65**: 668–674.
2. Parker CJR, Hunter JM. Dependence of the neuromuscular blocking effect of atracurium upon its disposition. *British Journal of Anaesthesia* 1992; **68**: 555–561.
3. Parker CJR, Hunter JM. A new four-parameter threshold model for the plasma atracurium concentration–response relationship. *British Journal of Anaesthesia* 1992; **68**: 548–554.
4. Fisher DM, Canfell PC, Fahey MR, Rosen JI, Rupp SM, Sheiner LB, Miller RD. Elimination of atracurium in humans: Contribution of Hofmann elimination and ester hydrolysis *versus* organ-based elimination. *Anesthesiology* 1986; **65**: 6–12.
5. Gibaldi M, Perrier D. *Pharmacokinetics*, 2nd Edn. New York: Marcel Dekker, 1982; 48.

6. Parker CJ, Hunter JM. Pharmacokinetics of atracurium. *British Journal of Anaesthesia* 1991; 67: 129–130.
7. Donati F, Varin F, Ducharme J, Gill SS, Theoret Y, Bevan DR. Pharmacokinetics and pharmacodynamics of atracurium obtained with arterial and venous blood samples. *Clinical Pharmacology and Therapeutics* 1991; 49: 515–522.
8. Hull CJ. A model for atracurium? *British Journal of Anaesthesia* 1983; 55: 95–96.

Sir,—The criticism by Dr Fisher of our method to calculate the V^{ss} of atracurium is the same as that previously raised by Parker and Hunter [1, 2]. We agree that our method does underestimate the true V^{ss}. However the V^{ss} we derived, which perhaps can best be termed the "apparent" or "functional" V^{ss}, is that which is required in conjunction with our estimate of the total clearance of atracurium at steady-state, for design of a bolus–infusion regimen [3]. We contend that derivation of parameters which predict dosing requirements is the primary goal of pharmacokinetic research. The true V^{ss} has no clinical use, as the time-dependent changes in the clearance of atracurium cannot be measured directly, and any hypothesized estimate may be the result of a significant modelling error.

The pharmacokinetic parameter estimates derived from the model proposed for atracurium by Fisher and colleagues are erroneous [4]. The slow initial sampling rates were insufficient to allow the model to take into account the contribution of the rapidly degraded isomers of atracurium [5]. Our own unpublished observations are consistent with those reported in the latter paper and suggest that 22.5% of the total dose of atracurium, components of the cis–trans and trans–trans isomers, undergo very rapid degradation in blood. The errors caused by the slow sampling rate were compounded by Fisher and colleagues using only samples obtained 25 min after the addition of atracurium in the analysis of their *in vitro* data. The contribution from these rapidly degraded isomers to the *in vitro* degradation of atracurium was totally neglected.

G. H. BEEMER
A. R. BJORKSTEN
D. P. CRANKSHAW
The Royal Melbourne Hospital,
Melbourne, Victoria 3050

1. Beemer GH, Bjorksten AR, Crankshaw DP. Pharmacokinetics of atracurium during continuous infusion. *British Journal of Anaesthesia* 1990; 65: 668–674.
2. Parker CJ, Hunter JM. Pharmacokinetics of atracurium. *British Journal of Anaesthesia* 1991; 67: 129.
3. Shanks CA. Pharmacokinetics of the non-depolarizing neuromuscular relaxants applied to the calculation of bolus and infusion regimens. *Anesthesiology* 1986; 64: 72–86.
4. Fisher DM, Canfell PC, Fahey MR, Rosen JI, Rupp SM, Sheiner LB, Miller RD. Elimination of atracurium in humans: contribution of Hofmann elimination and ester hydrolysis *versus* organ-based elimination. *Anesthesiology* 1986; 65: 6–12.
5. Tsui D, Graham GG, Torda TA. The pharmacokinetics of atracurium isomers *in vitro* and in humans. *Anesthesiology* 1987; 67: 722–728.

Sir,—We thank Dr Fisher for the interest which he has shown in our recent articles in the *British Journal of Anaesthesia* [1, 2], and we are grateful for the opportunity to reply. Dr Fisher raises two main points of difficulty: first the calculation of V^{ss}; second, the formulation of the new, threshold, pharmacodynamic model.

The calculation of V^{ss} as usually defined is, as Dr Fisher points out, subject to difficulties because of the elimination of atracurium from sites outwith the sampled (plasma) compartment, and the solution of this difficulty would require knowledge of the extent of peripheral degradation of the drug. This still remains unknown, although Fisher has estimated the rate of peripheral degradation from the rate of degradation in plasma *in vitro*. Whilst his approach may well represent an advance over methods which do not use such a correction, we have at least two reservations concerning it. First, atracurium undergoes ester hydrolysis to some extent, and the activity of esterases in tissues may not be identical to the activity of esterases in plasma. Second, the greater concentration of proteins in plasma than in interstitial fluid ensures a distribution of diffusible ions which falls short of equality, with a greater concentration of hydrogen ions in the plasma than in the interstitial fluid [3].

We agree with Fisher that our estimates of V^{ss}, in common with those of Beemer, Bjorksten and Crankshaw [4], are subject to error on this account, and it was for this reason that we stated exactly how we obtained the values of V^{ss}, and that these are estimates ([2] "Data analysis", paragraph 3). We do not feel that this seriously calls into question the utility of the results in the context of that paper, for the standard formula for V^{ss} at least allows standardized comparison of the data in volume terms. The purpose of the paper was to demonstrate, across a range of individuals, that drug effect is dependent on disposition. This is almost routinely assumed to be the case for the non-depolarizing neuromuscular blocking drugs and, of course, is implicit in the attempt to formulate a pharmacodynamic model. Direct evidence on this point is, as we pointed out in the introduction to the paper, rather scant, and the demonstration which is given in our paper of the correlation between the pharmacokinetic and pharmacodynamic data sets materially adds to the evidence which is available in this paradigm.

The second area of interest is the threshold term of the pharmacodynamic model, concerning which Dr Fisher raises several points:

(1) We agree that it would have been preferable to have used arterial rather than venous blood samples. We did not do so because the patients we studied were healthy, and were not about to undergo very major surgery. However, we must correct the suggestion that the systematic error in fitting the standard model is an artefact arising from the use of venous samples. On the contrary, venous samples *underestimate* the arterial plasma concentration to which the site of action is exposed during onset, for two reasons: first, because they are "downstream" at a time of increasing plasma drug concentration; second, because extraction of drug by the tissues ensures that venous concentrations are smaller than arterial during onset of block. If anything, the site of action was exposed to a *greater* drug concentration than that which we measured, during the period of the "onset discrepancy". Any systematic error arising from the use of venous samples thus militated against the discovery of a threshold, and we would have perhaps found a stronger case for postulation of a threshold, and greater values of $C_{\mathrm{P}}^{ss}{}_{0}$, had we used arterial samples.

(2) Perhaps the most important point concerns the calculation which Dr Fisher presents of the effect of the drug at a concentration close to our estimate of $C_{\mathrm{P}}^{ss}{}_{0}$. We agree that a concentration of 120 ng ml^{-1} produces little twitch depression, and this is predicted by the standard model, *if* one assumes a value of gamma approximately 4. For example, if one applies a concentration of 120 ng ml^{-1}, mentioned by Dr Fisher, to the standard logistic equation, with a $C_{\mathrm{P}}^{ss}{}_{50}$ of 360 ng ml^{-1}, and gamma of 4, then:

$$\text{Effect} = \frac{120^4}{120^4 + 360^4} \times 100 \approx 1.2\%.$$

The value of gamma which Dr Fisher must have used in his calculation is close to what one obtains if one fits the standard model. Unfortunately, to fit an inappropriate model may lead to inappropriate parameter values, and it is precisely gamma which decreases in value when one restructures the standard model to include a threshold. The greater values of gamma which are obtained with the standard model are the means by which the standard model obtains a small value of effect when effect site concentrations are relatively great. We can see no other reason for proposing or holding onto such a value of gamma, whilst we can see good reasons for proposing a threshold.

(3) Whilst effect site concentrations are hypothetical, and pharmacokinetic and pharmacodynamic models may represent "black boxes", we do not agree that they are black boxes of an entirely arbitrary structure. In our view, structural and statistical aspects of model building should go hand in hand. To accept the nihilistic suggestion that no single model can be valid or invalid implies that we should abandon the structural aspects of model building altogether and simply fit, say, a polynomial to our data set. This would, however, fail to advance our understanding of what factors are quantitatively responsible for drug actions, and we do not feel that Dr Fisher would seriously entertain this logical conclusion of his proposition.

(4) Dr Fisher makes the interesting suggestion that a more complicated link model might be necessary to explain the

relationship between plasma concentration and effect. We would agree that the assumption of first-order intercompartmental drug transfer is a simplification of what must obtain in the muscle *in vivo*, and it may be that further refinement of the link model will bring closer agreement between observations and model predictions. Such refinement would add further model parameters, and, in our view, these will require simultaneous justification from both structural and statistical points of view.

We are delighted by the interest which Dr Fisher has shown in our work, but we fail to see that there is a flaw in the justification for the threshold model which we have proposed.

C. J. R. Parker
J. M. Hunter
Royal Liverpool University Hospital
Liverpool

1. Parker CJR, Hunter JM. A new four parameter threshold model for the plasma atracurium concentration–response relationship. *British Journal of Anaesthesia* 1992; **68**: 548–554.
2. Parker CJR, Hunter JM. Dependence of the neuromuscular blocking effect of atracurium upon its disposition. *British Journal of Anaesthesia* 1992; **68**: 555–561.
3. Pitts RF. *Physiology of the Kidney and Body Fluids*, 2nd Edn. Chicago: Year Book Medical Publishers Incorporated, 1972.
4. Beemer GH, Bjorksten AR, Crankshaw DP. Pharmacokinetics of atracurium during continuous infusion. *British Journal of Anaesthesia* 1990; **65**: 668–674.

SEDATION WITH PROPOFOL DURING REGIONAL ANAESTHESIA

Sir,—Diprivan (propofol) has been used extensively to sedate patients undergoing procedures with regional anaesthesia. However, its use to provide sedation, as distinct from anaesthesia, in association with regional anaesthesia is not an approved indication in every country. Recent unpublished information [1] has indicated that, in some instances, sedation with propofol in patients given regional anaesthesia for surgical procedures can be associated with bradypnoea or hypoxaemia, or both. A reduction in oxygen saturation has been reported by Patterson and colleagues in patients given propofol for sedation whilst undergoing upper gastrointestinal endoscopy [2]. In view of these observations, oxygen saturation should be monitored in all such patients, with oxygen supplementation readily available for provision where clinically indicated.

ICI also wish to remind clinicians that propofol should be given only by those trained in anaesthesia and not those directly involved in the conduct of surgical or diagnostic procedures.

B. D. C. Arnold
ICI Pharmaceuticals
Macclesfield

1. Data on file. Macclesfield: ICI Pharmaceuticals.
2. Patterson KW, Casey PB, McEllistrem RF, Murray JP, Cunningham AJ. Haemodynamic and oxygen saturation changes during upper gastrointestinal endoscopy: evaluation of propofol and midazolam sedation. *British Journal of Anaesthesia* 1989; 62: 222P–223P.

ASPIRIN, BLEEDING TIME AND CENTRAL NEURAL BLOCK

Sir,—We write in support of the views expressed by Drs O'Kelly and Lawes [1] on the limited usefulness of the bleeding time as a clinical screening test in patients receiving aspirin therapy who are candidates for central neural blocks. Our own detailed views have been published elsewhere [2] and we shall not repeat them here. However, we are concerned that Dr McDonald maintains her dogmatic support [3] of the use of the bleeding time and that Professor Bromage suggests that it may be medico-legally imprudent not to perform this test [4]. We would remind them that there are two entirely separate matters being considered here. First, does aspirin therapy increase the risk of spinal haematoma? Second, is the bleeding time a clinically useful indicator of the amount of platelet dysfunction produced by aspirin therapy? Even if the answer to the latter question is in the affirmative, this does not imply that aspirin therapy increases the risk of spinal haematoma. That question can only be answered by long-term epidemiological studies. At the moment there are no data, only opinions.

J. A. W. Wildsmith
J. H. McClure
Royal Infirmary
Edinburgh

1. O'Kelly SW, Lawes EG. Bleeding time. *British Journal of Anaesthesia* 1992; **69**: 330–331.
2. Wildsmith JAW, McClure JH. Anticoagulant drugs and central nerve blockade. *Anaesthesia* 1991; **46**: 613–614.
3. McDonald R. Bleeding time. *British Journal of Anaesthesia* 1992; **69**: 329.
4. Bromage IR. Bleeding time. *British Journal of Anaesthesia*. 1992; **69**: 330.

DEATH CERTIFICATION

Sir,—I found Dr Baskett's review of cardiopulmonary resuscitation helpful and informative [1]. However, he perpetuates a common misconception about certification of death. He states that (non-medical personnel) "are not qualified to certify death". In the U.K., this is incorrect. If Dr Baskett cares to examine a death certificate, he will find that there is still space to indicate that the body was not seen after death by a medical practitioner. Statements such as his will encourage bystanders, professional or not, to undertake futile, undignified and psychologically hurtful cardiopulmonary resuscitation when it is plain that it would be pointless.

It is unhelpful for an expert reviewer to preach the uncritical application of cardiopulmonary resuscitation, which is already widespread and too often inappropriately attempted.

A. C. Skinner
Warrington

1. Baskett PJF. Advances in cardiopulmonary resuscitation. *British Journal of Anaesthesia* 1992; **68**: 182–193.

Sir,—Thank you for asking me to comment on Andrew Skinner's letter. He may be technically correct in his review of the contents of the death certificate. However, I was dealing with the reality of U.K. practice, particularly with nurses in hospital who require prior instructions from a senior doctor in charge of the patient before implementing a "do not resuscitate" order. I was urging that consultants and other senior doctors make such a decision before their patients suffer cardiac arrest, and communicate their instruction to the nursing staff. Doctors would seem to be abandoning their responsibility if they left such decisions to the nursing staff. More extensive use of a hospital "do not resuscitate" policy for patients in whom resuscitation is inappropriate should go some way towards achieving Dr Skinner's (and my own) aim of reducing the number of futile and undignified resuscitation attempts.

The situation outside hospital is slightly different because, in the majority of cases, prior medical instructions have not been issued. There may be a few instances in which the family doctor has given guidance to the relatives. However, I believe that the ambulance service, in the absence of knowledge of the patient's prior health status, should be instructed to proceed with resuscitation with the exception of obvious cases such as decapitation, incineration or rigor mortis, *etc*.

P. J. F. Baskett
Frenchay Hospital
Bristol

KETOROLAC POSTOPERATIVE ANALGESIA

Sir,—I read with interest the article "Ketorolac for postoperative analgesia after orthopaedic surgery" [1]. Currently, we are undertaking a similar study investigating the morphine-sparing effect of ketoprofen after total knee replacement. I wish to make the following comments:

First, a fixed i.m. dose of morphine is not the ideal way to determine the amount of opioid needed to investigate a morphine-sparing effect of any drug [2]. The total dose of morphine given by this route is dependent on patient–nurse communication and nursing response, and this is mentioned in the discussion [1].

The aim in any pain study is to test the severity of pain and quality of pain relief experienced by the patient during the postoperative period. Two assessments of pain over 24 h may not be enough to give an adequate idea of the quality of pain. Baseline assessment at the time of arrival from theatre, before any analgesic injection is given, is essential. Pain relief scores at more frequent assessments should have been added (beside visual analogue (VAS) and verbal pain scores) to improve the sensitivity of these tests in detecting the amount of resulting pain relief.

From baseline assessments, the pain intensity difference (PID) and summed PID could have been calculated, both of which have been shown to be more sensitive [3] in revealing significant differences when VAS failed to do so.

Last, controlling another factor—the nature of the operation—might be prudent in any controlled pain study. The authors did not specify the type of operations, but classified them as only major and minor surgery according to specific criteria. These do not rule out the possibility of patients within the same category having a different quality of pain.

A. AL-HASANI
Leicester Royal Infirmary
Leicester

1. Kinsella J, Moffat AC, Batrick A, Prentice JW, McArdle CS, Kenny GNC. Ketorolac trometamol for postoperative analgesia after orthopaedic surgery. *British Journal of Anaesthesia* 1992; **69**: 19–22.
2. Notcutt WG. Wound infiltration and Caesarean section. *Anaesthesia* 1991; **46**: 999.
3. Power I, Noble DW, Douglas E, Spence AA. Comparison of i.m. ketorolac trometamol and morphine sulphate for pain relief after cholecystectomy. *British Journal of Anaesthesia* 1990; **65**: 448–455.

Sir,—It is true that the use of a fixed i.m. dose of morphine is not the ideal method to study the morphine-sparing effects of a drug. Ketorolac has been shown to produce a morphine-sparing effect in other studies. The study in question was designed to see if there was any significant reduction in the use of morphine when this was prescribed in the usual manner in our hospital after orthopaedic surgery. This approach may be more relevant to clinical practice, as the use of patient-controlled analgesia is unlikely to be the standard method of providing analgesia for all patients in the near future.

I am surprised at the suggestion that pain measurements should have been made before any analgesics were given. All patients received intraoperative morphine and either ketorolac or placebo at the end of surgery, as we felt that to withhold analgesia for the purpose of studying pain would be unethical. The use of more frequent pain assessments may be of value, but could also influence the patient's demand for analgesia. This study aimed to reproduce the routine postoperative care as closely as possible, whilst making sufficient observations from which valid con-

[redacted]

arean section under general anaesthesia but her medical history was otherwise unremarkable, with no history of opioid abuse. Preoperative assessment included instructions on the use of a PCAS for postoperative pain relief.

Intraoperative management with spinal anaesthesia was uneventful, with no complaint of discomfort during the procedure. A PCAS (Graseby) was attached to the patient's i.v. infusion with an Abbott Mini-Bore PCAS giving set. The PCAS was loaded with a 50-ml syringe containing morphine sulphate 2 mg ml^{-1}. It was programmed with a bolus dose of 1 mg, a lock-out time of 3 min and no background infusion.

Eight hours after the operation, anaesthetic advice was sought, because there was only 6 ml of solution remaining in the syringe. The patient was fully conscious, with a ventilatory frequency of 16 b.p.m. She still complained of slight pain on movement, but none at rest.

The PCAS chart revealed that the patient had used 89 mg of morphine over the 8 h after surgery. The consumption per hour was as follows: first 1 h 12 mg, second 1 h 3 mg, third 1 h 25 mg, fourth 1 h 16 mg; over the next 4-h period another 33 mg of morphine. No programming error was found on the PCAS. There was no evidence of extravasation of morphine. At this stage, the patient admitted to giving the hand device to her husband during visiting, and had asked him to press the switch every 3 min. It had seemed an ideal way of getting good analgesia without having to rouse herself from slumber to press the switch.

The patient was warned how inappropriate and potentially dangerous this practice is. The PCAS was refilled and reprogrammed with a lock-out time of 6 min. The nursing staff were asked to watch for ventilatory depression, and the patient was monitored with a pulse oximeter. She remained pain free at rest and only had slight pain on movement over the next 16 h. She consumed an additional 21 mg of morphine. Sp_{O_2} remained at 97% with FI_{O_2} 0.28.

This case differs from others reported [2, 3] in that the patient required no resuscitation, and the unusually large dose of opioid was administered by her husband. This case demonstrates that we must continue to emphasize strongly that the P in PCAS means patient and not by proxy.

F. Y. LAM
Rotherham District Hospital
Rotherham

1. Notcutt WG, Knowles P, Kaldas R. Overdose of opioid from patient-controlled analgesia pumps. *British Journal of Anaesthesia* 1992; **69**: 95–97.
2. Farmer M, Harper NJ. Unexpected problems with patient-controlled analgesia. *British Medical Journal* 1992; **304**: 574.
3. Johnston T, Daugherty M. Oversedation with patient-controlled analgesia. *Anaesthesia* 1992; **47**: 81–82.

VETERINARY USE OF "XYLOCAINE" SPRAY

Sir,—The Association of Veterinary Anaesthetists wishes to draw attention to a problem experienced in cats with the new formulation of the pump pack Xylocaine Spray (Astra Pharma-

USE OF THE LARYNGEAL MASK AND FACE MASK BY INEXPERIENCED PERSONNEL

Sir,—Tolley, Watts and Hickman have demonstrated apparently that the laryngeal mask airway (LMA), when inserted by inexperienced personnel, is less satisfactory for ventilation of the lungs than use of a traditional mask and airway [1]. We believe that their results warrant careful examination, because they conflict with previous studies which demonstrate that LMA insertion is learned readily by inexperienced personnel [2, 3]. There are some features of the study that cause us some concern and may make the results less valid than they might have been.

Although the operators are stated to be junior hospital doctors with no postgraduate anaesthetic experience, there is no information on whether or not they had received resuscitation training, either when medical students or after qualification. We understand from the several Australian trainees in our department that it is common practice in Australian medical schools for undergraduates to undergo basic resuscitation training which includes the use of bag and mask ventilation.

Patients who were likely to present difficulties for tracheal intubation were excluded. We would be interested to know what criteria were used and if any of the patients included in the study actually presented difficulty when the trachea was intubated after the study manoeuvres were completed (this is a situation in which the LMA has a well recognized role) [4]. It is not stated how the operators were instructed to use the face mask and airway. Use of a mannequin or demonstration *in vivo* may make the technique easier to learn than using a video. Also, the operators were not taught in a standard fashion to use the LMA: some watched a video, while others were demonstrated the technique by an investigator.

Patient selection and anaesthetic management were not strictly standardized, with a large age range of 18–84 yr (ASA I–III) and there was no direct monitoring of the state of neuromuscular block. The spread of patient age and general health may not directly affect results in this study; however, we are concerned that there was no standard muscle relaxation, when variations in muscle tone could affect the ease of ventilation by inexperienced personnel using each technique.

Although the required tidal volume of 800 ml was recommended by the American Heart Association, the source of the time limit of 40 s is not mentioned. We are intrigued by the decision to record the times of all the failures as 41 s and then quote the results as a mean time to successful ventilation. Additional useful information would have included the ranges of the time to successful ventilation. Although the difference in mean times to ventilation is statistically significant, it is interesting to debate if the approximately 5-s delay with the LMA is clinically significant, bearing in mind the "hands free" security of the airway and the degree of protection against aspiration that the LMA potentially affords. It would also be interesting to know the exact causes of failure in both groups. Was it desaturation to less than the limit of 95 %, or was it difficulties with LMA placement (or the fit of the mask in the other group)?

The fact that each operator managed the airways, using both techniques, of five patients would enable the authors to examine the learning curve for each technique. We would be interested to know if there was any reduction in time taken to successful ventilation as experience was gained and, if so, if the improvement was equal with each technique.

This study compared LMA ventilation and use of the mask and airway yet, during resuscitation, initial ventilation is with the face mask and airway using a large inspired concentration of oxygen. The next phase is to control and protect the airway by intubating the trachea with a tracheal tube. The exact role of the LMA in resuscitation has yet to be elucidated fully, but we feel that it is possible that the LMA may be a useful adjunct for airway management, especially when the operator is inexperienced. The degree of protection against aspiration afforded by the LMA and its stability within the airway during external cardiac massage need to be determined. We hope that the questionable results of this study will not deter investigators from examining in more detail the exact role of the LMA during resuscitation.

M. B. Walker
A. P. L. Goodwin
C. Verghese
Royal Berkshire Hospital
Reading

1. Tolley PM, Watts ADJ, Hickman JA. Comparison of the use of the laryngeal mask and face mask by inexperienced personnel. *British Journal of Anaesthesia* 1992; **69**: 320–321.
2. Pennant JH, Walker MB. Comparison of the endotracheal tube and laryngeal mask in airway management by paramedical personnel. *Anesthesiology* 1992; 74: 531–534.
3. Davies PRF, Tighe SQM, Greenslade GL, Evans GH. Laryngeal mask airway insertion by unskilled personnel. *Lancet* 1990; **336**: 977–979.
4. Benumof JL. Management of the difficult adult airway. *Anesthesiology* 1991; **75**: 1087–1110.

Sir,—Tolley, Watts and Hickman [1] compared ventilation with the laryngeal mask and face mask by inexperienced personnel. Their data do not support the statement appearing in the summary that "the LMA cannot be recommended as a resuscitation device for use by inexperienced operators". Having failed to address most of the relevant questions, they are quite unjustified in making categorical statements about the place of the LMA during cardiopulmonary resuscitation.

Some of the *theoretical* advantages of the LMA compared with the Guedel airway and face mask during cardiopulmonary resuscitation are as follows: avoidance of anatomical airway obstruction, maintenance of a seal between the device and the airway and freeing of the operator's hands for other activities (such as cardiac massage, cervical spine control and two-handed bag squeezing). Therefore, ventilation *should* be greater *in the long term*, particularly by the single operator. None of these issues has been addressed adequately by Tolley and colleagues, who have examined the first 40 s of ventilation only, without cardiac massage or resuscitation.

Against these supposed advantages must be balanced the disadvantages of the LMA, namely: the time necessary for insertion and the resultant loss of ventilation, the difficulty of insertion, the possibility of a greater risk of aspiration of stomach contents [2] and the loss of the airway seal when compliance is reduced, such as during external cardiac compression.

Success rates of 74 % and 92 % are reported for the LMA and face mask groups, respectively, and it is inferred that the reason for failure to achieve two tidal volumes of 800 ml within 40 s in the LMA group was delayed insertion. We have recorded an LMA insertion rate of 94 % by inexperienced operators within the same time, using the production of carbon dioxide as the end-point [3]. This suggests that Tolley's junior doctors were inadequately trained or were particularly unskilful, or that our results were inaccurate. Our trainees carried out twice the number of insertions and their performance was very similar to that recorded for anaesthetists on first exposure [4, 5]. We do not believe that our results are inaccurate. Despite the lack of a significant learning curve for LMA insertion [3], it is still necessary to include at least some "hands-on" experience during training. Additionally, as junior doctors, they would have had much more practical experience of ventilation with a face mask than with an LMA. Therefore, it would seem that Tolley's high LMA failure rate represents inadequate training and that, if a more realistic success rate had been achieved, the difference recorded between techniques would have been substantially reduced and perhaps eliminated.

Not only should the study have been carried out after adequate training, rather than during it, but it should also have been extended over a clinically relevant period—for several minutes—when insertion has been successful within 40 s. It is possible that the LMA would allow more ventilation than the face mask over a longer period, making good the losses necessitated by insertion, as known from the inadequacies of single operators using a face mask, Guedel airway and resuscitation bag [6, 7].

This study poses an important question, but as a result of both failure to train adequately and an inappropriate period of assessment, its conclusions are not justifiable. The LMA may or may not be useful during resuscitation, but more carefully conducted research is needed before it is written off for this purpose.

S. Q. M. Tighe
Royal Naval Hospital
Plymouth

1. Tolley PM, Watts ADJ, Hickman JA. Comparison of the use of the laryngeal mask and the face mask by inexperienced

personnel. *British Journal of Anaesthesia* 1992; **69**: 320–321.

2. Barker P, Langton JA, Murphy PJ, Rowbotham DJ. Regurgitation of gastric contents during general anaesthesia using the laryngeal mask airway. *British Journal of Anaesthesia* 1992; **69**: 314–315.
3. Davies PRF, Tighe SQM, Greenslade GL, Evans GH. Laryngeal mask airway and tracheal tube insertion by unskilled personnel. *Lancet* 1990; **336**: 977–979.
4. Maltby JR, Loken RG, Watson NC. The laryngeal mask airway: clinical appraisal in 250 patients. *Canadian Journal of Anaesthesia* 1990; **37**: 509–513.
5. Brodrick PM, Webster NR, Nunn JF. The laryngeal mask airway. A study in 100 patients during spontaneous breathing. *Anaesthesia* 1989; **44**: 238–241.
6. Jesudian MCS, Harrison RR, Keenan RL, Maull KI. Bag and mask ventilation; two rescuers are better than one: preliminary report. *Critical Care Medicine* 1985; **13**: 122–123.
7. Greenslade GL. Single operator cardiopulmonary resuscitation in ambulances. *Anaesthesia* 1991; **46**: 391–394.

Sir,—We are grateful for the opportunity to reply to the points made in these letters. The aim of the study was to assess the use of the LMA by inexperienced operators with the intention that it be available on general wards for use by nurses and junior doctors in emergencies. Training these large numbers of staff to use the device would necessarily be brief. The operators in our study had all trained at the same medical school and had received a short period of resuscitation training as undergraduates. This usually involved only a small amount of "hands on" experience of airway management. However, our proposed users in emergencies on wards would all be expected to have had a similar small amount of previous experience with face mask and bag, and perhaps none with patients. The inexperienced operators to whom Dr Tighe refers were naval medical trainees who had a short training programme using mannequins. The fact that the success rates differ reflects only that different populations were studied, and no inaccuracy need be invoked to explain it. With the LMA, his inexperienced group performed as well as anaesthetists, and ours did not. The group we used and the training given seemed to us to be a reasonable representation of the final ward users and the depth of training they can expect.

No specific criteria were used to exclude patients who might present with difficult tracheal intubation, but the investigators who recruited patients erred on the side of caution in their choice. None of the patients presented difficulty with intubation subsequently. Operators were shown how to use the mask and airway by demonstration by one of the investigators. Although the means of demonstration, age ranges and degree of neuromuscular block were not standardized, we feel that the crossover design of the study, with each patient being subjected to both airway management techniques in random order, effectively excluded any potential bias caused by these factors.

Reasons for failure in the mask group were not recorded, but were mainly as expected: an inability simultaneously to maintain a seal and a clear airway. All the failures in the LMA group were caused by jamming of the mask at the posterior pharyngeal wall. Times and failure rates for the first and fifth attempts for each operator were not statistically different, so no learning effect was demonstrated. It is of interest that in only two patients was the LMA successful where the face mask had failed, whereas there were 11 patients in whom the reverse was true.

The source of the 40-s cut-off time was the paper by Davies and colleagues [1]. We agree that 40 s is a very short time; however, for reasons of patient safety the time was accepted to reduce the risk of desaturation. As there were no episodes of desaturation during the trial, a less conservative time might be allowed in future. The ranges of times were 15–40 s for the LMA and 14–40 s for the bag and mask. We felt that, although a difference in mean times of only 5 s is probably not clinically significant, the difference in failure rate was. In other words, the added long-term advantage of the LMA is lost if it cannot be inserted at all. It is possible that this difference would disappear if more time was allowed, but are we going to advise users to persevere with attempts to insert the LMA after 40 s without success when the patient is apnoeic, while with the face mask they may have delivered two or three breaths of 100% oxygen in this time?

Our conclusion was based on the results and conditions in this trial, which were intended to imitate use by inexperienced ward staff with minimal training. We believe that the results indicate that the LMA is not suitable as a first line airway management tool to be used by staff who have had only a brief demonstration of its use. This does not preclude its use as a second line of management by staff with more training, as in the paper by Davies and colleagues [1].

We agree that the LMA deserves further consideration for emergency airway management, for the reasons given. Further work might also define if the use of expired tidal volumes, as in our paper, or detection of end-tidal carbon dioxide as in the paper of Davies and colleagues, is a more accurate measure of adequate ventilation.

P. Tolley
A. Watts
J. Hickman
Wrexham Maelor Hospital
Wrexham

1. Davies PRF, Tighe SQM, Greenslade GL, Evans GH. Laryngeal mask airway insertion by unskilled personnel. *Lancet* 1990; **336**: 977–979.

CHANGES IN HAEMODYNAMIC VARIABLES WITH THIOPENTONE, METHOHEXITONE, PROPOFOL AND ETOMIDATE

Sir,—I read with interest the paper by Price and colleagues [1], and I agree that their results may indicate that etomidate produced some degree of myocardial depression, as has been shown by other investigators [2, 3]. However, I believe that their study design precludes comparison with other induction agents because they did not account for the effects of either changes in blood-gas tensions or the accompanying medications (nitrous oxide and alfentanil).

Both hypoxaemia and hypercapnia may increase cardiac output and decrease systemic vascular resistance. Because thiopentone, methohexitone and propofol depress ventilation more than etomidate [4, 5], the different results in these groups possibly could be explained by hypoventilation and hypoxaemia. This could have occurred in these patients, as $F\text{I}_{O_2}$ was 0.3, ventilation was assisted only after 30 s of apnoea and, because there was no documentation that either ventilatory frequency or tidal volume were measured, it seems possible that both could have been less than optimal for the maintenance of normal blood-gas tensions.

Also, the combination of alfentanil and nitrous oxide may have depressant effects on cardiac output [6] and should have been used as a control to establish if the effects in the etomidate group were attributable to the administration of these drugs. Until the above issues are addressed, I believe that the conclusions drawn from their results are probably invalid.

E. L. Williams
University School of Medicine
St Louis, U.S.A.

1. Price ML, Millar B, Grounds M, Cashman J. Changes in cardiac index and estimated systemic vascular resistance during induction of anaesthesia with thiopentone, methohexitone, propofol and etomidate. *British Journal of Anaesthesia* 1992; **69**: 172–176.
2. Firestone S, Kleinman CS, Jaffe CC, Taunt RT, Schneiderman S, Talner NS, Barash PD. Human research and noninvasive measurement of ventricular performance: an echocardiographic evaluation of etomidate and thiopental. *Anesthesiology* 1978; **51**: S22.
3. Criado A, Maseda J, Navarro E, Escarpa A, Avello F. Induction of anaesthesia with etomidate: a study of 36 patients. *British Journal of Anaesthesia* 1980; **52**: 803–805.
4. Choi SD, Spaulding BC, Gross JB, Apfelbaum JL. Comparison of the ventilatory effects of etomidate and methohexital. *Anesthesiology* 1985; **62**: 442–447.
5. Streisand JB, Nelson P, Bubbers S, Stocking-Korzen R, Posthuma W, East KA, Gillmor ST, Stanley TH. The respiratory effects of propofol with and without fentanyl. *Anesthesia and Analgesia* 1987; **66**: S171.
6. Stanley TH, Liu W-S. Cardiovascular effects of meperidine–nitrous oxide anaesthesia before and after pancuronium. *Anesthesia and Analgesia* 1977; **56**: 669–673.

Sir,—Thank you for the opportunity of replying to the comments of Dr Williams. The design of a study to examine cardiovascular changes during induction of anaesthesia is difficult. Our initial aim was to examine the effects of the anaesthetic induction agents alone. Our pilot study showed that doses of the induction agent sufficient to induce anaesthesia in unpremedicated patients resulted in anaesthesia of less than 3 min. We decided therefore to supplement anaesthesia with other agents used commonly in clinical practice. As supplementary drugs were given to all study groups, we feel that the observed pharmacological differences may be interpreted as those produced by the anaesthetic induction agents.

The ventilatory differences between the drugs used in our study again make study design difficult. Hypoxaemia and hypocapnia produce cardiovascular effects, although I am uncertain of their relevance over the time scale of our study. Intermittent positive pressure ventilation (IPPV) also produces cardiovascular effects. To minimize this between drugs with differing ventilatory depressant effects, an apnoeic period of 30 s was chosen.

Increases in Pa_{CO_2} over the period of the study are unlikely to have been significant, as ventilation was assisted using a Bain circuit with a high fresh gas flow to minimize rebreathing. A pulse oximeter was used in the majority of patients and hypoxaemia, which occurred rarely, was transient.

M. Price
St Mary's Hospital
London

ANTEPARTUM ASSESSMENT FOR ANAESTHESIA

Sir,—In response to the letter by Cody and Johnston [1], we offer our solution for reducing the likelihood of unanticipated anaesthetic problems occurring out of hours when senior help may not be readily available.

In our department, a simple card file system has been in operation for the past 10 years. This was initiated after episodes of "failure of communication" occurred, the obstetricians being reluctant or insensitive of the need to divulge information relevant to the potential anaesthetic management of an obstetric emergency. However, the problem of communication between anaesthetic staff was also found to be at fault in several cases. Patients are entered into the card file via three main routes: (1) At antenatal clinic where the obstetrician identifies a potential anaesthetic risk or problem, such as previous lumbar laminectomy, scoliosis, major neurological, cardiovascular or respiratory disease. (2) Patients attending the antenatal clinic who volunteer information concerning problems that have occurred during previous surgical procedures or confinements at other hospitals, for example pseudocholinesterase deficiency, bleeding disorders, or complicated extradural placement. (3) Patients who have had unanticipated complications in their anaesthetic management in our own department, such as problems establishing extradural or subarachnoid block, difficult or failed intubation, allergy or anaesthetic drug sensitivity.

In the first two cases, patients are seen during the same antenatal clinic visit by a member of the anaesthetic department, usually a consultant. The potential problem is established, and an outline plan for their management is recorded on a filecard with basic obstetric details, including likely date of confinement. The period after consultation permits correspondence with other hospitals to obtain old notes and to request appropriate specialist advice. In the third instance, details of the anaesthetic problem encountered and its solution are recorded in case of a future confinement.

The merit of this simple system is that it is easy to use and update. It is available in the anaesthetic office area adjacent to the delivery suite theatres, and trainee anaesthetists are encouraged to browse through the card file. "Pending" problems (those patients approaching term) are filed separately at the front of the file; other cards are filed alphabetically. Any patient whose name appears on our card file system is issued with a yellow sticker which is applied to the front of their notes. This indicates that when the patient is admitted the on-call anaesthetic staff are to be informed. After delivery, in the event of anaesthetic intervention, the nature of the management and the outcome are recorded by the attending anaesthetist. Equally relevant is the observation that no anaesthetic involvement was required.

We have found that, in a hospital with approximately 6600 deliveries annually, we have successfully reduced, but not eliminated, the incidence of the 'phone call which concludes "and by the way..."

D. R. Uncles
L. E. S. Carrie

John Radcliffe Hospital
Oxford

1. Cody MW, Johnston JA. Antenatal assessment for anaesthesia. *British Journal of Anaesthesia* 1992; **69**: 332.

Sir,—I have every sympathy with Drs Cody and Johnston [1] over their difficulty in persuading obstetricians and midwives to refer expectant mothers with medical problems for anaesthetic consultation. The need for *antenatal* referral, for example for diaphragmatic hernia or congenital heart disease diagnosed *in utero*, is much rarer. To achieve prompt referral for a *maternal* problem, two hurdles must be overcome. First, those seeing the mother during pregnancy must spot the problem and, second, the need for anaesthetic referral must spring to mind. It is a sad fact that in many centres one or both of these hurdles may not be overcome, possibly because a mother may rarely see an obstetrician or visit hospital for antenatal care. Nevertheless, to see *every* booked mother would be a major undertaking in many units, beyond the scope of anaesthetic departments.

I attempt to solve the problem by writing an angry letter every time we are taken by surprise as were Drs Cody and Johnston, and by setting aside a regular time each week for anaesthetic referral.

F. Reynolds
St Thomas' Hospital
London

1. Cody MW, Johnston JA. Antenatal assessment for anaesthesia. *British Journal of Anaesthesia* 1992; **69**: 332.

Sir—Thank you for the opportunity to reply to Dr Reynolds' letter.

The problem of mothers not attending for antenatal visits is, I believe, beyond the anaesthetic remit. However, with the greatest extradural rates up to 50% and with an increasing Caesarean section rate there may be a case for seeing mothers antenatally. I wonder if informed consent or explanations given in the heat of labour would be valid in the current litiginous era.

M. Cody
J. Johnston
Erne Hospital
Enniskillen

British Journal of Anaesthesia 1993; **70**: 117–118

BOOK REVIEWS

Adult Respiratory Distress Syndrome. Edited by A. Artigas, F. Lemaire, P. M. Suter and W. M. Zapol. Published by Churchill Livingstone, Edinburgh. Pp. 535; illustrated; indexed. Price £90.00.

This multi-author book on the *Adult Respiratory Distress Syndrome* (ARDS) brings together more than 100 contributors, 75% of whom are based in Europe and the remainder in North America. The book is divided into sections on Clinical Aspects, Morphology, Pathophysiology, Lung Water, Pulmonary Circulation, Pulmonary Function, Mechanical Ventilation, Therapy and Future Trends. It was astonishing to find that no definition of ARDS was given until chapter 47, the last chapter in the book. It was also surprising to read the old chestnut in the third line of the first chapter that there are 150000 cases of ARDS per annum in the U.S.A.—this oft-quoted guess made in 1972 puts the incidence of ARDS 10 times greater than that found in recent surveys—not a reassuring start to an authoritative text.

There was little new material in the section on morphology, although there was a very good chapter by Bachofen and colleagues with beautiful electron micrographs showing extensive destruction of the alveolar epithelium. This was followed by a good section on pathophysiology, with eight chapters on various aspects of this important subject. However, despite the fact that there were good reviews by well known workers in the field, all had the patina of age with few, if any, references after the early 1980s. The section on lung water content and capillary circulation was disappointing; in spite of the compelling evidence that alveolar epithelial destruction is the cardinal feature of ARDS, chapter after chapter discusses *microvascular* permeability. There was little or no discussion of corticosteroids, surfactant, nitric oxide, lung repair or of active transport across the alveolar capillary barrier. Reflection coefficient was not indexed and was mentioned only superficially. Permeability of the alveolar capillary barrier was also not indexed, and there was no mention of studies published in the past 6 years on barrier permeability in ARDS to ^{99m}TcDTPA or labelled albumin. The remainder of the book included a number of essays of interest to a few specialized workers who are already *au fait* with this work.

The penultimate and final chapters are likely to be of most interest to clinicians, although the section on future trends was rather dated. The reviewer concluded that the book is out of date and consequently cannot be recommended. A review article on ARDS published in this journal 2 years ago provides a more useful contemporary *résumé* of the subject.

J. G. Jones

Collection d'Anesthésiologie et de Réanimation, Volume 30: Monitorage Non-Invasif en Réanimation. Edited by G. Annat and F. Clergue. Published (1992) by Masson, Paris. Pp. 168; indexed; illustrated. Price FFr 275.00.

Since the publication of the first volume in 1984, the *Collection d'Anesthésiologie et de Réanimation* has compiled an excellent series of monographs on various topics in anaesthesia and intensive care. It is probably one of the most common books which French speaking anaesthetists read to keep up with the most recent trends in their specialty.

Monitorage Non-Invasif en Réanimation, Volume 30 of the collection, is no exception. It covers most aspects of non-invasive monitoring of critically ill patients in 10 chapters. These chapters provide good reviews on cardiovascular (four chapters) and respiratory (six chapters) monitoring.

The topics covering non-invasive measurement of cardiac output (J. L. Vincent) and the use of echocardiography in intensive care (F. Jardin) are excellent and very informative. I thoroughly enjoyed the chapter on the continuous measurement of $\dot{V}O_2$ and $\dot{V}CO_2$ during mechanical ventilation. Metabolic monitoring of critically ill patients undoubtedly will change the whole concept of nutritional management of intensive care patients.

However, the book seems to lack a chapter on non-invasive monitoring of the central nervous system, even if I do understand the Editors' choice in limiting the book to cardiovascular and respiratory monitoring. What I also found annoying was the multitude of spelling mistakes throughout the book, especially in the reference section.

On the whole, this is a book which I would gladly recommend to those with an interest in intensive care. It should be particularly useful for the trainee anaesthetist (at least those who are fluent in French) for the clinical measurement part of the Fellowship exam.

B. Appadu

MCQs in Anaesthesia: Basic Sciences. Edited by B. Kumar. Published by Butterworth-Heinemann Ltd, Oxford. Pp. 226. Price £12.95.

The aim of this book is to provide practice multiple choice questions for candidates preparing for the Part 2 F.R.C.Anaes. examination in pharmacology and physiology. The book contains 366 five-part questions. The answers and a brief explanation are provided on the reverse side of each page.

The questions are divided into nine sections covering the central nervous system (123 questions), cardiovascular (66), respiratory (56), endocrine (42), gastrointestinal (16), renal and hepatic (22) systems, and the topics haemopoiesis (14), acid–base status (17) and statistics (10). Within each section there are pharmacology and physiology questions. The distribution of questions seems reasonable and the standard of difficulty is appropriate. In the CNS section, there are 96 pharmacology questions and only 27 physiology, but pharmacokinetics, local analgesics and muscle relaxants are also included in this section. In the other sections, the balance between physiology and pharmacology is better, although the important subject of the cardiovascular system has only 66 stem questions.

This book would benefit from an introduction describing the negative marking system and providing some evidence on answering technique and self-testing. In general, this is a useful book for candidates preparing for the Part 2 F.R.C.Anaes. examination and I would recommend it to them.

C. S. Reilly

Key Topics in Anaesthesia. Edited by T. M. Craft and P. M. Upton. Published by Bios Scientific Publishers, Oxford. Pp. 298; indexed. Price £14.95.

The stated aim of this book is to provide an outline of subjects encountered commonly in the Part 3 F.R.C.Anaes. examination.

The book addresses 100 topics, listed alphabetically, which the authors suggest are common topics in the examination. Each subject is covered in 2–3 pages in a problem-oriented manner and the anaesthesia problems are dealt with under a series of headings. Suggested further reading is given at the end of each topic and consists of one or two key references.

The scope of this book is rather ambitious, with two authors attempting to provide comprehensive and authoritative summaries on a very diverse range of subjects. On reading some of the subjects with which I have clinical involvement, I found some areas where the information was inadequate and, in the case of carcinoid, outdated.

I am unsure of the role of this book. It is certainly no basis for preparation for study for the Part 3 F.R.C.Anaes. examination, as it does not cover all the subjects. Any candidate preparing for the examination will have to undertake their own background reading of all the subjects. Making use of this book would be rather like using someone else's notes—always an unsatisfactory method. The possible value of this book is as a check that a subject has been covered, or as a comforter immediately before the examination for last minute reference.

C. S. Reilly

Hypoxia, Metabolic Acidosis and the Circulation. Edited by A. I. Arieff. Published (1992) by Oxford University Press, Oxford. Pp. 215; illustrated; indexed. Price £45.00.

The quality of this series of monographs from the American Physiological Society is such that one comes to expect that they will be comprised of definitive up-to-date reviews of the chosen field. In this present volume on various aspects of the biochemical and physiological consequences of hypoxia, the reviews are as usual exhaustive and authoritative, but not always up-to-date. The book springs from a FASEB meeting in 1988 and while some of the chapters cite references as recent as 1990, several have none more recent than 1988 or 1989, suggesting that there has been some delay in publication.

The volume is divided into two sections, the first on the pathophysiology of hypoxia and metabolic acidosis and the second on clinical manifestations of hypoxia. The former section reviews experimental and clinical studies on the effects of hypoxia on the intact circulation and on the normal and compromised heart. This is of current relevance to the increasing interest in the effects of postoperative hypoxaemia on the heart.

The major concern of the second section is lactic acidosis as a consequence of circulatory failure, particularly when it is a result of cardiac arrest, rather than hypoxia *per se*. It will be of interest to those treating such patients, particularly the final three chapters on the treatment of the condition with alkalinizing agents.

This volume will be a welcome addition to the shelves of departmental libraries, despite the relative lack of recent references. It will make a useful starting point for those with an interest in this field and provide a springboard to the current literature.

C. D. Hanning

Moving to Audit, An Educational Package for Hospital Doctors and General Practitioners. C. Arnold, J. Bain, R. A. Brown, R. M. Harden, J. M. Laidlaw, S. McAleer and R. A. Wood. Published (1992) by: The Postgraduate Office, Ninewells Hospital and Medical School, Dundee. Pp. 128; glossary; illustrated. Price: £29.00 (Challenges, Activities, Resource Book and Personalized Feedback); £12.50 (Resource Book only).

The "package" consists of a research manual plus the option to receive "challenges" over the next 6 months. The manual is A4 size and 128 pages of large print entitled "What every doctor needs to know about Medical Audit". The 12 chapters start with definition, work through misconceptions and benefits through to planning. Sampling, measurement and data collection are all discussed, followed by storage, confidentiality and computers. The manual concludes with chapters on data description, interpreting of statistics and keeping audit going. Two sample challenges are included; these establish elaborate "real-life" scenarios to make rather trivial educational points and seem of minor value.

The manual itself is good. It is aimed primarily at general practitioners, but there is much that could be of value to anaesthetists and it is also very suitable for nursing staff and paramedical personnel. It is well presented with clearly marked key messages, questions directed at the reader, follow-up activities and boxed, short case studies. It is easy to read and the references and further reading at the end of each chapter are particularly good.

The basic audit cycle of observation of practice leading to establishment of standards (or a desired performance level), then intervention, followed by re-observation is well known. Many anaesthetic departments are currently embarking on massive data collection exercises as "audit". This book discusses the need for objectives so that the audit produces more than a mass of percentages. Among the important points discussed are co-operation, the need for audit to be non-threatening, that actual benefit must be possible from data collection and what should be studied should be both feasible and affordable. It recommends that small areas be audited. The emphasis is on improving medical care, with only one paragraph mentioning the use of audit for increasing the bargaining power of a group for resources. This seems appropriate; costing exercises are not necessarily audit.

The chapter on questionnaire design is very practical. The statistics sections are designed only to demystify the area so would-be auditors feel happier about reaching for the detailed texts. One area that is not addressed is the role of the professional researcher and statistician. The emphasis of the text is that audit is for everyone! Only once, on page 106, it is rather simplistically suggested: "If you are in any doubt about the statistics to use ask someone who has plenty of experience in sorting out such problems." This is a slight worry. It is one thing for staff to work on improving patient satisfaction with a GP appointments system, but audit procedures which are not always of research quality are now being used to make major professional and financial decisions, and perhaps some caution on this point should have been suggested.

In summary: this is a well written and useful book for those beginning audit procedures.

C. Jorm and L. Strunin

ERRATUM

The authors regret and apologize for their unintentional omission of acknowledgements for financial support given by The Association of Anaesthetists of Great Britain and Ireland for research, leading to publication of the following manuscripts:

Reeder MK, Muir AD, Foëx P, Goldman MD, Loh L, Smart D. Postoperative myocardial ischaemia: Temporal association with nocturnal hypoxaemia. *British Journal of Anaesthesia* 1991; **67**: 626–631.

Reeder MK, Goldman MD, Loh L, Muir AD, Casey KR. Haemodynamic effects of periodic respiration: abolition with supplementary oxygen. *British Journal of Anaesthesia* 1991; **67**: 326–328.

Reeder MK, Goldman MD, Loh L, Muir AD, Foëx P, Casey KR, McKenzie PJ. Postoperative hypoxaemia following major abdominal vascular surgery. *British Journal of Anaesthesia* 1992; **68**: 23–26.

Papers for publication and all editorial communications should be addressed to the Editor, University Department of Anaesthesia, Leicester Royal Infirmary, Leicester LE1 5WW; business communications to the Publishers: Professional & Scientific Publications Ltd, BMA House, Tavistock Square, London WC1H 9JR.

The GUIDE TO CONTRIBUTORS may be found in the advertisement section of this issue (pages ii, iv & vi).

Published monthly. Annual subscriptions: Worldwide £125.00; USA only $198.00 (direct orders only). Trainee rate: Worldwide £69.00. Airmail rates on application. ISSN 0007–0912. Orders must be accompanied by payment; cheques should be made payable to Professional and Scientific Publications. Orders and payments should be sent to Professional and Scientific Publications, BMA House, Tavistock Square, London WC1H 9JR. Orders in the United States of America may be sent to Professional and Scientific Publications, Box 560B, Kennebunkport, Maine 04046.

Group Advertisement Director, Mr R. Hayzen.
Advertisement Manager, Mrs S. Rowe.
Publishing Manager, Mr D. Shaw.
BMA House, Tavistock Square, London WC1H 9JR. 071-387 4499.

Whilst every effort is made by the publishers and editorial committee to see that no inaccurate or misleading data, opinions or statement appears in this Journal, they wish to make it clear that the data and opinions appearing in the articles and advertisements herein are the responsibility of the contributor or advertiser concerned. Accordingly, the publishers and the editorial committee and their respective employees, officers and agents accept no liability whatsoever for the consequences of any such inaccurate or misleading data, opinions or statement. Whilst every effort is made to ensure that drug doses and other quantities are presented accurately, readers are advised that new methods and techniques involving drug usage, and described within this Journal, should only be followed in conjunction with the drug manufacturer's own published literature.

© Copyright: 1993 *British Journal of Anaesthesia*
All rights reserved. No part of this publication may be reproduced, stored in a retrieval system, or transmitted in any form by any means, electronic, mechanical, photocopying, recording or otherwise, without the prior permission of the *British Journal of Anaesthesia*.

Published by Professional and Scientific Publications.
Printed in Great Britain by the University Press, Cambridge.

"*I would have everie man write what he knowes and no more.*"—MONTAIGNE

BRITISH JOURNAL OF ANAESTHESIA

VOLUME 70, No. 2 FEBRUARY 1993

EDITORIAL I

UPPER AIRWAY REFLEXES

Upper airway reflexes are of great practical importance to anaesthetists. Coughing during anaesthesia may often be only a minor problem, but can occasionally be a serious danger. Aspiration of foreign material into the lungs when pharyngeal coordination and airway reflexes are impaired can cause serious sequelae. Fortunately, although aspiration may be a relatively frequent event after anaesthesia [1], serious complications appear to be rare [2]. Much is known of the components of airway reflexes, but the application of this knowledge to everyday practice is surprisingly patchy. How can we learn more about the impact of anaesthesia on these reflexes?

At first sight, the reflex appears simple. Irritation of receptors in the upper respiratory tract causes a reflex motor response. The receptors of the respiratory tract include slowly adapting ("stretch") receptors responsible for the Hering–Breuer reflex, and rapidly adapting ("irritant") receptors, which are activated briefly by light touch, dust, chemical stimuli and cold air [3]. It is the rapidly adapting receptors that are responsible for the cough reflex. Their afferent impulses run in the vagus nerve, the superior laryngeal branch of which carries afferents from within the upper larynx; the central reflex site is in the medulla, and the efferent impulses are again carried in the vagus to the laryngeal muscles, and by the appropriate nerves to respiratory muscles (diaphragm, intercostal, accessory and abdominal muscles). Some other reflexes involving the larynx are well known by anaesthetists: the "Brewer–Luckhardt" reflex [4] is quoted in old anaesthetic textbooks. This is the response of vocal cord adduction ("laryngeal spasm") that occurs frequently after surgical stimuli such as anal dilatation. However, it is unlikely that any reflex is simple [5]. Further examination of the components of the upper airway reflexes may emphasize this.

Laryngeal afferent neurones with receptive fields in the epiglottis can be activated by a range of stimuli, but mechanical stimuli are most effective, particularly a light touch that moves over several receptive fields [6]. The sensory units consist of free nerve endings that lie between the mucosal cells of the airway epithelium [7]. They can respond faithfully up to high frequencies [8]. More than 50% of laryngeal afferent fibres also respond to cooling or, more exactly, to rate of heat loss from the airway [9]. They also respond to the presence of fluids, particularly water [10], and a variety of chemicals. The response to fluids appears to have a considerable degree of chemical discrimination: isotonic sodium chloride causes very little in the way of stimulation, whereas water, or solutions that are isosmolar but free of chloride ions, are potent stimuli for the laryngeal mucosal receptors [11]. The pattern of nerve firing from epiglottic receptors depends on the nature of the fluid causing the stimulation: low osmolality fluid contact leads to a longer delay and a longer period of activity than a solution that contains no chloride. Similarly, the response after ammonium chloride solution, for example, causes a more high-frequency and rapidly adapting response in a single superior laryngeal nerve fibre than most other substances [12], and it has been suggested that an "afferent portal" in the brainstem decodes these activity patterns before further central projection occurs. Inhalation of isosmolar solutions that lack chloride causes cough; if the solution is not isosmolar, then it causes not only cough, but also bronchoconstriction in susceptible subjects. This latter response is not affected by inhaled lignocaine, suggesting that the mechanisms for these two airway responses are different, despite stimulation of neurally similar receptors [13].

Sensory units appear to be particularly abundant over the arytenoid cartilages and are also found on the laryngeal side of the epiglottis [14]. The superior laryngeal nerve carries a large proportion of small diameter myelinated fibres (group III, A delta or B sensory fibres) [9], which carry afferent impulses from rapidly adapting receptors from structures such as the epiglottis [15].

The recurrent laryngeal nerve also carries sensory fibres [16], mainly from rapidly adapting receptors that are activated by light touch. These receptors are particularly numerous at the anterior and posterior extremities of the inferior surface of the vocal cords. Stimulation of these receptors results in vocal cord movement [17]. Afferent fibres in the laryngeal nerves project centrally to the nucleus tractus solitarius, particularly the caudal and posterior parts [6].

The vagal nerves do not represent the only pathway for airway protective reflexes: for example, potassium chloride applied to the lungs of anaesthetized dogs results in ipsilateral expiratory muscle activity despite section of the vagi, suggesting a spinal reflex via sympathetic afferent nerves [18].

Cough consists of an initial laryngeal opening, followed by a closure of both the glottis and the supraglottic structures; the structures then open and vibrate, and the epiglottis may move forcibly backwards and then forwards again [19].

Laryngeal closure is a complex muscular event, involving activity of muscles that are considered to have abductor effects when active alone. Activation of the laryngeal muscles by stimulation of the internal branch of the superior laryngeal nerve, which causes reflex laryngeal closure, results in a more forceful closure than stimulation of the recurrent laryngeal nerve, which activates the laryngeal muscles directly, but presumably in a less co-ordinated way [20].

Cough does not always follow stimulation of laryngeal receptors, even in susceptible species [21]. In sleeping infants, introduction of small quantities of warm saline into the pharynx, sufficient to cause pooling posterior to the larynx, rarely leads to cough, and more commonly to apnoea and a swallow reflex [22].

The strength of reflex response to laryngeal stimulation appears experimentally to vary with the depth of anaesthesia [23]. The reaction of airways to inhaled substances is reduced by increased mucus secretion, presumably because the mucus protects the airway surface [24]. In contrast, viral infection of the lungs leads to increased airway responsiveness, with amplification of reflex bronchoconstriction involving both afferent and efferent pathways, as discussed by Jacoby and Hirshman [25]. Changes in inspiratory flow rate alter the reaction to inhaled irritant aerosol [26] and may alter the reaction to inhaled ammonia, as discussed by Murphy and coworkers [27].

Using inhaled dilute concentrations of ammonia, Duckett and Hirsh [28] studied 23 patients before surgery, of whom 11 agreed to a repeat study either 24 h after surgery or 24 h after removal of a tracheal tube. Treatment was not allocated randomly and did not appear comparable, but their abstract concluded that tracheal intubation was responsible for a significant reduction in the competence of the glottic reflex.

The motor response to inhalation of a small concentration of ammonia consists of temporary inhibition of inspiration—probably phrenic—and a brief partial adduction of the vocal cords, although inspiratory flow does not cease completely. Greater concentrations can cause coughing. How good a paradigm is this response for the cough reflex?

First, the exact location of the receptors involved is unclear. Although receptors that respond to ammonia have been detected on the epiglottis, and within the larynx, the lower airways are also well supplied with receptors that respond to irritant substances with a rapidly adapting pattern of discharge [29]. Ammonia in concentrations about 100–200 p.p.m. stimulates both continuously active and normally silent laryngeal receptors, but only after a delay of between 2 and 4 s [30]. In lightly anaesthetized patients, insufflation into the nose of a 5% concentration of volatile anaesthetics such as halothane, and particularly enflurane and isoflurane, can cause reflex responses. The duration of expiration increases and the larynx tightens [31].

Thus it is likely that all parts of the airway are involved in the response to inhaled ammonia: the sensation of ammonia inhalation is subjectively localized generally within the larynx and trachea. The sensitivity of the reflex was reduced by local anaesthesia of the airway, but the anaesthesia was extensive, involving injection via the cricothyroid membrane, and thus did not localize any particular receptive field [32].

Second, the stimulus used does not closely resemble a natural stimulus such as foreign material in the airway; finally, the response used as an end-point is not a cough.

Commonly, coughing is caused by entry of foreign material into the larynx and lower airways—that is "something going down the wrong way". The term *laryngeal competence* is often taken to imply, not only an adequate cough response in response to foreign material, but also that the upper airway is sufficiently well co-ordinated to prevent material getting down into the larynx and lower airways in the first place. Impairment of this co-ordination is a frequent accompaniment of recovery from general anaesthesia, and is of particular concern when regurgitation is likely, such as after lower oesophageal resection. The ability to protect the airway returns as central reflex impairment decreases; it is probable that the reflex response to ammonia inhalation does the same. Do interventions such as sedation or general anaesthesia specifically impair airway co-ordination or responsiveness, and the reflex response to inhaled foreign material, more than other reflexes or other indices of central depression such as reaction time? The influences of different anaesthetics appear to vary considerably. For example, the effects of inhaled anaesthetic vapour depend upon the circumstances. A conscious patient can usually breathe 5% halothane vapour without coughing, when requested to do so for the purpose of inhalation induction, but after a "sleep dose" of thiopentone the same patient would cough vigorously if even 1% halothane were inhaled. Since barbiturates do not obviously affect the activity of the airway receptors, it seems that in the conscious state the central reflex is less easily activated. In contrast, the gag reflex is equally vigorous in awake and thiopentone-anaesthetized subjects. Other anaesthetic agents such as propofol have a more depressant effect on upper airway reflexes [33], and animal studies have shown changes in patterns of laryngeal muscle activity with sleep state and barbiturate anaesthesia [34]. The cough reflex is more easily elicited in some species than in others [21].

In consequence of all these factors, it appears unlikely that there will be a constant relationship between tests such as reaction time, and tests of airway reactivity such as ammonia inhalation, when different agents such as barbiturates, benzodiazepines and propofol are investigated, particularly if different species are used. The ideal anaesthetic in this regard would suppress reflex responses such as cough, whatever the stimulus, during anaesthesia and allow rapid recovery after emergence. At first sight, propofol might appear to be valuable, but it appears to have a surprisingly prolonged effect on other respiratory reflexes [35], and it may be that the reflex protection of the airway is similarly impaired for a prolonged period. Indeed, volatile anaesthetics may finally prove to be superior. Cough responses remain, at least at light levels of anaesthesia. During anaesthesia with enflurane (1.5% end-tidal), instillation of small quantities of water into the trachea can evoke reflex responses such as forceful expiration, coughing, panting and apnoea. I.v. lignocaine reduces the panting, coughing and expiratory reflexes, probably by a central action [36]. However, the central actions of different anaesthetics can result in widely different laryngeal responses [37].

Clearly, further study of "laryngeal competence", its components and the effects of anaesthesia and sedation are required. This would be aided by a test of how well a patient can prevent "things going down the wrong way", and of how well things can be coughed out if they do. Ideally this test should not require invasive measurements, patient co-operation or ionizing radiation. The method refined by Langton and his colleagues [38] is a step in the right direction, but it may be necessary to use several paths to reach the goal.

G. B. Drummond
Edinburgh

REFERENCES

1. Tiret L, Desmonts JM, Hatton F, Vourch'h G. Complications associated with anaesthesia: a prospective survey in France. *Canadian Anaesthetists Society Journal* 1986; **33**: 336–344.
2. Cheney FW, Posner KL, Caplan RA. Adverse respiratory events infrequently leading to malpractice suits. *Anesthesiology* 1991; **75**: 932–939.
3. Widdicombe JG. Pulmonary and respiratory-tract receptors. *Journal of Experimental Biology* 1982; **100**: 41–48.
4. Brewer N, Luckhardt AB, Lees WM, Bryant DS. Reflex of glottis by stimulation of visceral afferent nerves. *Anesthesia and Analgesia* 1934; **13**: 257–259.
5. Sherrington C. *The Integrative Action of the Nervous System*, 2nd Edn. New Haven: Yale University Press, 1947; 116.
6. Sweazey RD, Bradley RM. Responses of neurons in the lamb nucleus tractus solitarius to stimulation of the caudal oral cavity and epiglottis with different stimulus modalities. *Brain Research* 1989; **480**: 133–150.
7. Sato M, Koyano H. Autoradiographic demonstration of the distribution of vagal-afferent nerve fibers in the epiglottis of the rabbit. *Brain Research* 1987; **410**: 101–105.
8. Davis PJ, Nail BS. Quantitative analysis of laryngeal mechanosensitivity in the cat and rabbit. *Journal of Physiology (London)* 1987; **388**: 467–485.
9. Jammes Y, Nail B, Mei N, Grimaud C. Larygeal afferents activated by phenyldiguanide and their response to cold air of helium-oxygen. *Respiration Physiology* 1987; **67**: 379–389.
10. Sampson S, Eyzaguirre C. Some functional characteristics of mechano-receptors in the larynx of the cat. *Journal of Neurophysiology* 1964; **27**: 464–480.
11. Boggs DF, Bartlett D. Chemical specificity of a laryngeal apneic reflex in puppies. *Journal of Applied Physiology* 1982; **53**: 455–462.
12. Bradley RM, Stedman HM, Mistretta CM. Superior laryngeal nerve response patterns to chemical stimulation of sheep epiglottis. *Brain Research* 1983; **276**: 81–93.
13. Eschenbacher WL, Boushey HA, Sheppard D. Alteration of the osmolarity of inhaled aerosols cause bronchoconstriction and cough, but absence of a permeant anion causes cough alone. *American Review of Respiratory Disease* 1984; **129**: 211–215.
14. Storey AT. A functional analysis of sensory units innervating epiglottis and larynx. *Experimental Neurology* 1968; **20**: 366–383.
15. Andrew BL. A functional analysis of the myelinated fibres of the superior laryngeal nerve of the rat. *Journal of Physiology (London)* 1956; **133**: 420–432.
16. Hirose H. Afferent impulses in the recurrent laryngeal nerve in the cat. *Laryngoscope* 1961; **71**: 1196–1206.
17. Suzuki M, Kirchner JA. Sensory fibers in the recurrent laryngeal nerve. *Annals of Otology, Rhinology, and Laryngology* 1969; **78**: 21–31.
18. Coon RL, Clifford PS, Hopp FA, Zuperku EJ. Reflex ventilatory effects of KCl stimulation of lung receptors with sympathetic afferents. *Respiration Physiology* 1990; **82**: 349–358.
19. von Leden H, Isshiki N. An analysis of cough at the level of the larynx. *Archives of Otolaryngology* 1965; **81**: 616–625.
20. Murakami Y, Kirchner JA. Mechanical and physiological properties of reflex laryngeal closure. *Annals of Otology, Rhinology, and Laryngology* 1972; **81**: 59–71.
21. Korpas J, Tomori Z. Cough and other respiratory reflexes. In: Herzog H, ed. *Progress in Respiration Research* Vol. 12. Basel: Karger, 1979; 105.
22. Pickens DL, Schefft GL, Thach BT. Pharyngeal fluid clearance and aspiration preventive mechanisms in sleeping infants. *Journal of Applied Physiology* 1989; **66**: 1164–1171.
23. Miller AS, Dunmire C. Characterisation of the postnatal development of superior laryngeal nerve fibers in the postnatal kitten. *Journal of Neurobiology* 1976; **7**: 483–494.
24. King M, Kelly S, Cosio M. Alteration of airway reactivity by mucus. *Respiration Physiology* 1985; **62**: 47–59.
25. Jacoby DB, Hirshman CA. General anesthesia in patients with viral respiratory infections: an unsound sleep? *Anesthesiology* 1991; **74**: 969–972.
26. Barros MJ, Zammattio SJ, Rees PJ. The importance of inspiratory flow rate in the cough response to citric acid inhalation in normal subjects. *Clinical Science* 1990; **78**: 521–525.
27. Murphy PJ, Langton JA, Barker P, Smith G. Effect of oral diazepam on the sensitivity of upper airway reflexes. *British Journal of Anaesthesia* 1993; **70**: 131–134.
28. Duckett JE, Hirsh RA. Glottic competence in patients using 2% ammonia. *Anesthesiology* 1980; **53**: S193.
29. Widdicombe JG. Receptors in the trachea and bronchi of the cat. *Journal of Physiology (London)* 1954; **123**: 71–104.
30. Boushey HA, Richardson PS, Widdicombe JG, Wise JCM. The response of laryngeal afferent fibres to mechanical and chemical stimuli. *Journal of Physiology (London)* 1974; **240**: 153–175.
31. Nishino T, Tanaka, A, Ishikawa T, Hiraga K. Respiratory, laryngeal and tracheal responses to nasal insufflation of volatile anesthetics in anesthetized humans. *Anesthesiology* 1991; **75**: 441–444.
32. Hinkle JE, Tantum KR. A technique for measuring the reactivity of the glottis. *Anesthesiology* 1971; **35**: 634–637.
33. Langton J, Wilson I, Barker P, Smith G. Preliminary observations of vocal cord movements on induction of anaesthesia with propofol or thiopentone. *British Journal of Anaesthesia* 1990; **65**: 582–583P.
34. Sherry JH, Megirian D. State dependence of upper airway respiratory motoneurons: functions of the cricothyroid and nasolabial muscles of the unanesthetized rat. *Electroencephalography and Clinical Neurophysiology* 1977; **43**: 218–228.
35. Blouin RT, Conard PF, Gross JB. Time course of ventilatory depression following induction doses of propofol and thiopental. *Anesthesiology* 1991; **75**: 940–944.
36. Nishino T, Hiraga K, Sugimori K. Effects of i.v. lignocaine on airway reflexes elicited by irritation of the tracheal mucosa in humans anaesthetized with enflurane. *British Journal of Anaesthesia* 1990; **64**: 682–687.
37. Nishino T, Yonezawa T, Honda Y. Different laryngeal responses during respiratory arrest produced by hypoxia withdrawal, thiopentone, ketamine, and lidocaine in cats. *Anesthesiology* 1982; **56**: 280–285.
38. Langton JA, Murphy PJ, Barker P, Key A, Smith G. Measurement of the sensitivity of upper airway reflexes. *British Journal of Anaesthesia* 1993; **70**: 126–130.

British Journal of Anaesthesia 1993; **70**: 124–125

EDITORIAL II

THE LARYNGEAL MASK AIRWAY IN PAEDIATRIC PRACTICE

The laryngeal mask airway (LMA) has become extremely popular worldwide with anaesthetists for control of the airway in a wide variety of circumstances. Although about five times as many adult size LMA are sold as paediatric sizes, their use in children is becoming commonplace.

The LMA was developed after cadaveric studies in the adult [1]. The sizes available for paediatric use are scaled-down versions. The differences in airway anatomy between children, particularly infants, and adults suggest that a scaled-down version may not be as successful for younger subjects. Practical experience led clinical anaesthetists to request an interim size and the manufacturers now produce a size 2.5 for use in children weighing 20–30 kg.

Research into use of the LMA in paediatric practice has focused on the size 2. It was found in three studies that a clinically acceptable airway was obtained in 92–99 % of children weighing more than 6.5 kg [2–4]; this success rate is comparable to that found in studies in adults [5]. The incidence of minor problems on insertion and after removal of the LMA seems to be greater in children compared with adults. Several authors have commented that problems on insertion are often caused by inadequate anaesthesia and Mason and Bingham have recommended the use of an antisialagogue premedication [2].

One clear difference between adult and paediatric use of the LMA is the incidence of an imperfect position diagnosed by fibreoscopy. Rowbottom, Simpson and Grubb [4] reported partial airway obstruction in 19 % of children, compared with an incidence of 10 % in a series in adults reported by Payne [6]. Moreover, the epiglottis could be seen within the mask in 49 % of children in Rowbottom's study. While this does not seem to compromise the airway in the majority of spontaneously breathing children, it may account in part for greater difficulty during positive pressure ventilation, and may interfere with attempts to enter the trachea via the LMA with a tracheal tube or bougie. However, this latter technique has been described in the management of a child with Pierre Robin syndrome [7]. Several authors have reported success in cases of difficult airway caused by a variety of anatomical abnormalities (Pierre Robin [8], Treacher Collins [9], cleft palate [10]). Anaesthetists must remember that where the abnormality resides within the larynx itself, attempts to insert an LMA correctly are likely to fail.

Individuals have developed their own method of insertion [11–14]; however, those who ignore Brain's advice [15] and keep some air in the cuff may increase the chance of downfolding the epiglottis. When difficulty is encountered negotiating the tongue a rotating method, similar to that commonly used to insert a Guedel airway, may often prove useful [12, 13].

The LMA has been advocated for diagnostic laryngobronchoscopy [16, 17]. The vocal cords may be seen with a flexible instrument introduced via the LMA in a spontaneously breathing, anaesthetized patient and this is appealing. However, the fibrescope findings described above caution against use of this technique for diagnostic purposes in children, particularly in laryngomalacia, as the LMA may either distort the epiglottis or not permit inspection.

The LMA has also proved useful during radiotherapy [18], CT scanning and magnetic resonance imaging (MRI). The ability to avoid repeated tracheal intubation during radiotherapy is invaluable. However, Marjot has reported trauma to the pharyngeal wall after repeated use of an LMA [19] and subsequently investigated the pressure exerted. He found that the pressure exerted by the size 2 LMA upon the pharyngeal mucosa would exceed 60 mm Hg unless the inflation volume was much less than recommended [20]. Those who use the LMA for prolonged or repeated use should be aware of the possibility of damage to the pharynx. While this airway is apparently ideal for use during MRI, the metal spring in the valve may distort the image [21] and Fairfield has warned of possible problems during MRI spectroscopy [22]. A reinforced LMA was used successfully in a child who was required to be prone for radiotherapy [23].

The tendency for the original size 2 LMA to kink has been reduced in subsequent versions. However a flexible, reinforced LMA is now commercially available in all sizes except size 1. This new product is recommended for use in head, neck and dental surgery, including tonsillectomy. The manufacturers warn of greater resistance to breathing caused by smaller internal diameter (i.d.) and greater length. The reinforced size 2 LMA has a tube with an i.d. of 5.1 mm, compared with 7.0 mm for the ordinary LMA tube. Bhatt and colleagues have found that the non-reinforced LMA (all sizes) imposes less resistance and requires lower additional inspiratory work compared with the corresponding sized tracheal tube [24]. A similar study is required for the reinforced LMA.

Anaesthetists who are tempted to use the reinforced LMA when subsequent access to the airway is restricted must ensure that adequate airway monitoring is undertaken and that the surgeon is fully aware that any movement of the head, neck or drapes, insertion of a pack etc. that would be acceptable with a tracheal tube in place, may displace the LMA. As with the introduction of the LMA, clinical experience and controlled study should establish the place of the reinforced LMA, especially for intra-oral and pharyngeal surgery.

Published research to date has not studied the size 1 LMA in large numbers, but those who have examined this type urge caution in its use [25]. Relatively few are sold and this reflects a reluctance to use the device in small infants. The anatomical differences between infants and children imply that a satisfactory position is more difficult to achieve in infants. Thus positive pressure ventilation is less successful and, in particular, inflation of the stomach may be more likely.

The writer shares the concern of others [26–28] that increasing dependency on the LMA by trainee anaesthetists will result in a lack of experience and skill in managing with a face mask an awkward or obstructed airway in unconscious patients. The management of cases such as acute epiglottitis without this skill is impossible.

The LMA undoubtedly has become well established in paediatric practice. There is insufficient published work on IPPV or the use of the size 1 to advocate widespread use. The use of the LMA in children should remain the province of the experienced anaesthetist, who should ensure that more junior anaesthetists first gain experience in conventional airway management in children.

I. G. Wilson
Leicester

REFERENCES

1. Brain AIJ. The laryngeal mask—a new concept in airway management. *British Journal of Anaesthesia* 1983; 55: 801–805.
2. Mason DG, Bingham RM. The laryngeal mask airway in children. *Anaesthesia* 1990; 45: 760–763.
3. Bailie R, Barnett MB, Fraser JF. The Brain laryngeal mask. A comparative study with the nasal mask in paediatric dental outpatient anaesthesia. *Anaesthesia* 1991; 46: 358–360.
4. Rowbottom SJ, Simpson DL, Grubb D. The laryngeal mask in children. A fibreoptic assessment of positioning. *Anaesthesia* 1991; 46: 489–491.
5. Brodrick PM, Webster NR, Nunn JF. The laryngeal mask airway. A study of 100 patients during spontaneous breathing. *Anaesthesia* 1989; 44: 238–241.
6. Payne J. The use of the fibreoptic laryngoscope to confirm the position of the laryngeal mask. *Anaesthesia* 1989; 44: 865.
7. Chadd GD, Crane DL, Phillips RM, Tunell WP. Extubation and reintubation guided by the laryngeal mask airway in a child with the Pierre-Robin Syndrome. *Anesthesiology* 1992; 76: 640–641.
8. Denny NM, Desilva KD, Webber PA. Laryngeal mask airway for emergency tracheostomy in a neonate. *Anaesthesia* 1990; 45: 895.
9. Ebata T, Nishiki S, Masuda A, Amaha K. Anaesthesia for Treacher Collins syndrome using a laryngeal mask airway. *Canadian Journal of Anaesthesia* 1991; 38: 1043–1045.
10. Beveridge ME. Laryngeal mask anaesthesia for repair of cleft palate. *Anaesthesia* 1989; 44: 656–657.
11. Newman PTF. Insertion of a partially inflated laryngeal mask airway. *Anaesthesia* 1991; 46: 235.
12. Chow BFM, Lewis M, Jones SEF. Laryngeal mask airway in children: insertion technique. *Anaesthesia* 1991; 46: 590–591.
13. McNicol LR. Insertion of laryngeal mask airway in children. *Anaesthesia* 1991; 46: 330.
14. Leader GL. Facilitation of the insertion of the laryngeal mask. *Anaesthesia* 1991; 46: 987.
15. Brain AIJ. Studies on the laryngeal mask: first, learn the art. *Anaesthesia* 1991; 46: 417–418.
16. McNamee CJ, Meyns B, Pagliero KM. Flexible bronchoscopy via the laryngeal mask: a new technique. *Thorax* 1991; 46: 141–142.
17. Brimacombe J. The laryngeal mask airway and flexible bronchoscopy. *Thorax* 1991; 46: 740.
18. Grebenick CR, Ferguson C, White A. The laryngeal mask airway in pediatric radiotherapy. *Anesthesiology* 1990; 72: 474–477.
19. Marjot R. Trauma to the posterior pharyngeal wall caused by a laryngeal mask airway. *Anaesthesia* 1991; 46: 589–590.
20. Marjot R. Pressure exerted by the laryngeal mask airway cuff upon the pharyngeal mucosa. *British Journal of Anaesthesia* 1993; 70: 25–29.
21. Langton JA, Wilson IG, Fell D. Use of the laryngeal mask airway during magnetic resonance imaging. *Anaesthesia* 1992; 47: 532.
22. Fairfield JE. Laryngeal mask and magnetic resonance imaging—a caution. *Anaesthesia* 1990; 45: 995.
23. Wilson IG, Eastley R. A modification of the laryngeal mask airway. *Anesthesiology* 1992; 47: 532.
24. Bhatt SB, Kendall AP, Lin ES, Oh TE. Resistance and additional inspiratory work imposed by the laryngeal mask airway. *Anaesthesia* 1992; 47: 343–347.
25. Fawcett WJ, Ravilla A, Radford P. The laryngeal mask airway in children. *Canadian Journal of Anaesthesia* 1991; 38: 685–686.
26. Lanigan C. Hypoxia after dental anaesthesia. *British Journal of Anaesthesia* 1992; 68: 635.
27. Withington DE. The laryngeal mask airway in paediatric anaesthesia. *Anaesthesia* 1991; 46: 321.
28. Russel D. Trainee anaesthetists and the laryngeal mask airway. *Anaesthesia* 1991; 46: 701.

British Journal of Anaesthesia 1993; 70: 126–130

ORIGINAL ARTICLES

MEASUREMENT OF THE SENSITIVITY OF UPPER AIRWAY REFLEXES

J. A. LANGTON, P. J. MURPHY, P. BARKER, A. KEY AND G. SMITH

SUMMARY

We describe a method for measurement of the sensitivity of upper airway reflexes. The technique is based upon delivery of an irritant chemical stimulus (dilute concentrations of ammonia vapour) to the upper airway. The technique is non-invasive and uses equipment which is portable, allowing measurements to be made in the clinical environment. (Br. J. Anaesth. 1993; **70**: 126–130)

KEY WORDS

Airway. Measurement techniques: airway reflexes.

During induction of anaesthesia, heightened upper airway reflexes may lead to laryngospasm and airway obstruction, and during recovery from anaesthesia, rapid return of laryngeal and upper airway reflexes is important to protect the lower airway from aspiration. Laryngeal competence may be reduced after tracheal intubation [1–4] and may contribute to atelectasis and respiratory failure [2], especially in the elderly.

In early work, Hoglund and Michaelsson [5] attempted to measure the reactivity of the upper airway using small concentrations of ammonia vapour; 10 years later, Pontoppidan and Beecher [6] used a similar technique, but in both these studies, the concentration of ammonia vapour inhaled by the subject was not known accurately, and their results were variable and unreliable.

The aim of our study was to develop a method which would measure the sensitivity of upper airway reflexes reliably. We have modified a previously described method, and designed new portable equipment that allows measurements to be made in the clinical environment. The reliability of this technique was evaluated in normal volunteers.

SUBJECTS AND METHODS

Measurement system

Small concentrations of ammonia vapour were used as an irritant chemical stimulus. The subject's upper airway was exposed to single intermittent breaths containing a small concentration of ammonia and, by measurement of the inspiratory flow pattern, a measure of the sensitivity of the subject's upper airway reflexes was made. This was expressed as the threshold concentration, that is the smallest concentration of ammonia required to elicit a reflex response.

The system is shown diagrammatically in figure 1. A small concentration of ammonia vapour in air was produced in the ammonia limb of the breathing system by mixing air from an air pump flowing at 10 litre min^{-1} with an adjustable flow of ammonia in nitrogen. The ammonia was delivered via a flowmeter from a calibrated cylinder containing 3% ammonia in nitrogen. The breathing system was calibrated to deliver accurate concentrations of ammonia vapour in the range 0–3500 p.p.m. The gas mixture flowed via a reservoir bag and clear plastic tubing around the system, as indicated in the figure by the arrows.

A pneumatic two-way balloon valve (V) allowed the subject to breathe room air via limb B: on switching the pneumatic valve, the subject took a single breath from the ammonia in air limb A. The two-way pneumatic balloon valve (Hans Rudolph) was controlled by the investigator and allowed the mixture to be directed to the subject for *one breath*, or to pass around the system to a specially constructed absorber without the subject being aware of the change. The balloon valve had a low compliance and an inflation time of 45–60 ms and deflation time of 60–75 ms.

The switching device, pneumotachograph head and mouthpiece were supported by an adjustable arm and held at a height convenient to the subject's mouth with the subject in either the sitting or the supine position. A Gould pneumotachograph recorded inspiratory flow pattern onto a Gould 2022 chart recorder. The subject breathed through a close fitting mouthpiece, whilst wearing a noseclip, via one-way valves, and exhaled to atmosphere. Subjects wore dark goggles and listened to music via a pair of headphones so that they were unaware of the switching of the pneumatic valve.

The absorber contained crystals of sodium benzoate absorbed onto silica gel matrix. Ammonia

---

This article is accompanied by Editorial I.

J. A. LANGTON, F.R.C.ANAES.; P. J. MURPHY, F.R.C.ANAES.; P. BARKER, F.R.C.ANAES.; A. KEY, B.SC.; G. SMITH, B.SC., M.D., F.R.C.ANAES.; University Department of Anaesthesia, Leicester Royal Infirmary, Leicester LE1 5WW. Accepted for Publication: August 27, 1992.

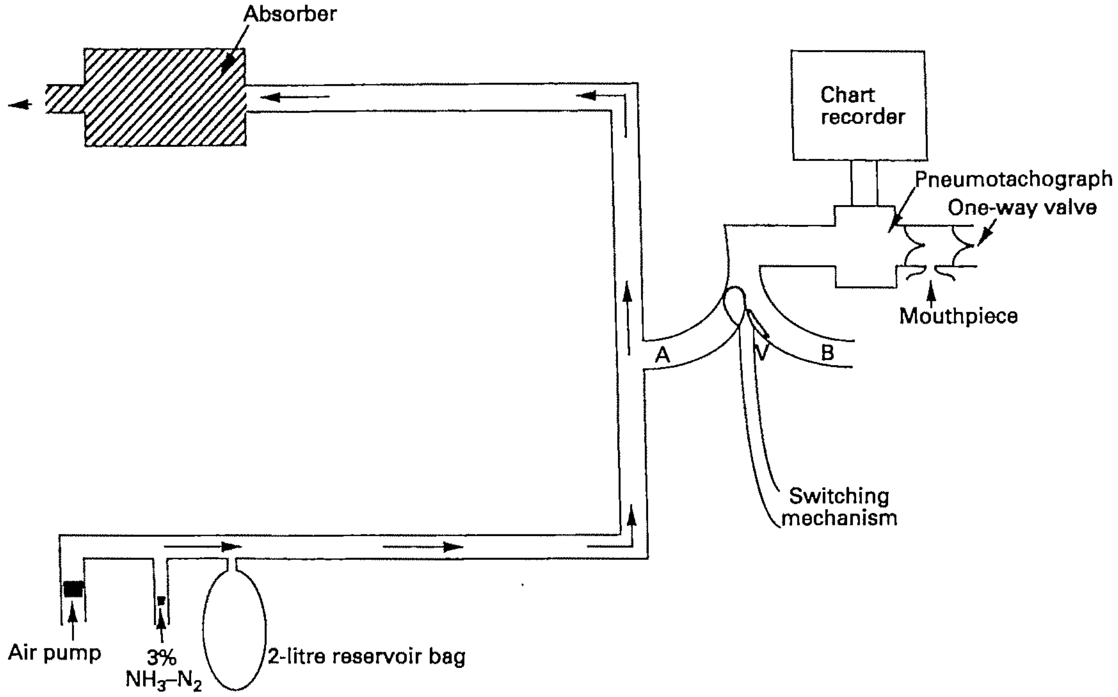


FIG. 1. Diagram of the equipment used to measure the sensitivity of upper airway reflexes. A = Ammonia–air limb; B = room air limb; V = balloon valve.

TABLE I. *Calibration data (mean († SEM; ‡ SD))*

Flowmeter setting	Measured flow (ml min^{-1})	Final [NH$_3$] (p.p.m.)	Time to 95% final [NH$_3$] (s)
50	73.1 (9.1)†	76 (12.3)‡	105
100	155.1 (1.02)	251 (12.6)	105
200	195.6 (0.85)	524 (33.7)	70
300	241.3 (0.54)	878 (17.8)	70
400	332.8 (0.88)	1140 (18.8)	70
500	427.1 (0.2)	1620 (61.5)	70
600	539.5 (2.95)	1970 (52.1)	70
700	635.5 (1.35)	2360 (60.4)	70
800	749.3 (0.63)	2790 (56.6)	70
900	863.7 (0.83)	3160 (142.2)	70
1000	964.6 (3.11)	3550 (170.2)	70

vapour in the carrier gas was removed by reaction with the crystals to produce ammonium benzoate and water. The crystals contained a marker dye which changed colour when the crystals were exhausted.

Calibration

Air. The air flow through the oxygen flowmeter was calibrated using a dry gas meter. With the flowmeter set at 10 litre min^{-1}, the total measured flow over a 30-min period was 324.9 litre (10.83 litre min^{-1}).

Ammonia–nitrogen. The flow of the 3% ammonia–nitrogen mixture via the cyclopropane flowmeter was measured using a bubble flowmeter (table I). The final ammonia concentration (p.p.m.), and the time (s) required for the concentration of ammonia to reach 95% of the final concentration were also recorded (table I). The concentration of ammonia produced in the system varied in the range 76–3550 p.p.m. at the differing flow rates. The time required to achieve 95% of the final concentration was 105 s at the slower flow meter settings of 50 and 100 ml; at faster flows, the time to reach 95% of the final concentration was 70 s.

The time for the ammonia concentration to decrease to zero after the ammonia–nitrogen flow was stopped was less than 2 min at all flow rates.

Ammonia–air. Small concentrations of ammonia in air were measured using a Bruel and Kjaer multigas analyser type 1302. The measurement principle used in this gas analyser is based on the photo acoustic infra-red detection method. The selectivity of the multigas analyser is determined by the optical filters installed. By studying the absorption spectra of gases to be monitored, the relevant optical filter is installed and the analyser zero calibrated and then span calibrated using the known certified ammonia concentration.

The Bruel and Kjaer multigas analyser was calibrated by the manufacturers to measure ammonia to a concentration of 10 p.p.m. (0.001%). The filter used was type 0976 with a centre wavelength 10.6 µm.

Initially, zero readings were obtained using a gas known not to contain ammonia vapour. The multigas analyser was then span calibrated using the certified gas concentration of 3.12% ammonia–nitrogen supplied by the British Oxygen Company. The breathing system was then calibrated in several stages. Measurements of the concentration of ammonia–air were made in the ammonia–air limb opposite the pneumatic switching valve (V).

The time to produce a reading and the concentration of ammonia in the circuit were measured. The air flow was set at 10 litre min^{-1}, the ammonia–nitrogen flow was started at 50 ml min^{-1} and recordings of ammonia concentration were started. Ten measurements were made over a period of 3–4 min. Then the ammonia–nitrogen flow was stopped and the time for the reading to decrease to zero was noted.

The calibration was performed at flows of ammonia–nitrogen 50 and 100 ml min^{-1} and then at increasing flow rates of ammonia–nitrogen in 100-ml increments up to a maximum of 1000 ml min^{-1}.

Volunteer studies

After obtaining Ethics Committee approval and informed written consent, we studied 10 healthy, non-smoking volunteers (eight male; ages 29–35 yr, weights 72–85 kg). The subjects were not taking any medication, were asked to refrain from drinking alcohol from noon the previous day, and were starved for 6 h before the study. We excluded subjects who were known asthmatics, and volunteers who were suffering from, or had a history of an upper respiratory tract infection within the previous 1 month.

Measurements of upper airway reactivity were made using the system described above.

The subject rested on a couch, wearing blackened goggles and listened to continuous loud music via a pair of headphones. A noseclip was applied and the subject was allowed to breathe through the mouthpiece via the one-way valve. The pneumatic switching valve was operated by the investigator at the end of expiration, so that the subject took one inspiratory breath from the ammonia limb.

The concentration of ammonia–air was increased in a stepwise manner in the ammonia limb (A), starting at the smallest concentration of ammonia. The threshold level of response to the ammonia stimulus was determined by the occurrence of a glottic stop, defined as a rapid decrease in the inspiratory flow, the flow decreasing by at least 25% of the peak inspiratory flow, followed by a swift recovery, the whole event lasting less than 0.5 s. An example of a glottic stop is shown in figure 2.

Each subject was investigated every 30 min for 4 h, and on six different days at least 1 week apart, in order to determine the reliability and repeatability of our measurements. In some subjects, we also presented the ammonia concentrations in a random order.

The deadspace of the equipment was calculated by measuring the volume of water required to fill it (48 ml).

RESULTS

Volunteers

The concentrations of ammonia vapour required to produce a glottic stop in each of the 10 volunteers are shown in table II.

The mean threshold of sensitivity of the upper airway was in the range of concentrations of ammonia 363–642 p.p.m. Statistical analysis (Mann–Whitney-*U* test) showed no significant differences between the measurements made repeatedly on one day compared with measurements made on separate days.

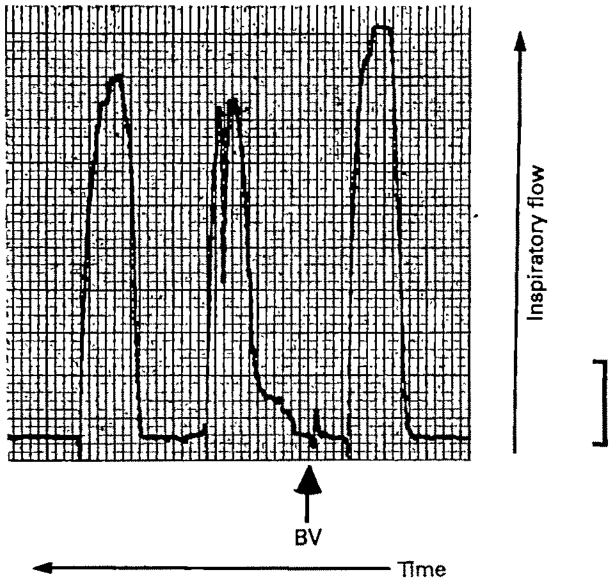


FIG. 2. An example of a glottic stop recording. BV = Switching of the balloon valve, allowing the subject to take one breath from the ammonia–air limb. Paper speed 30 cm min^{-1}; calibration bar = 10 litre min^{-1}.

TABLE II. *Threshold concentration of ammonia required to cause a glottic stop in 10 subjects (mean (median) [interquartile range])*

Subject	Threshold concn (p.p.m.) Different days ($n = 6$)	Same day ($n = 8$)
A	642 (524) [524–878]	465 (524) [376–524]
B	642 (524) [524–878]	499 (524) [524–674]
C	387 (387) [251–524]	363 (289) [251–524]
D	380 (387) [251–524]	471 (524) [327–524]
E	504 (524) [455–600]	435 (425) [327–524]
F	537 (524) [455–612]	544 (524) [524–674]
G	573 (524) [524–870]	440 (327) [327–524]
H	495 (524) [524–674]	536 (524) [524–600]
I	549 (524) [524–600]	536 (524) [524–543]
J	596 (524) [524–699]	627 (524) [524–678]

We found that, when the ammonia stimulus was presented in a random order rather than in an ascending challenge, the thresholds were the same, but the subjects found this to be considerably more unpleasant. Therefore this was performed in only five subjects.

DISCUSSION

Laryngeal reflexes are evoked by chemical or mechanical stimuli via receptors thought to be located in the hypopharynx and larynx [7]. Afferent pathways travel in both the parasympathetic and sympathetic nervous system and the motor response is temporary closure of the vocal cords [8]. In 1870, Kratschmer [9] demonstrated that mechanical and chemical irritation of the laryngeal and nasal mucosa caused reflex glottic closure and this reflex is now termed the Kratschmer reflex.

Hoglund and Michaelsson [5] described a technique for eliciting the Kratschmer reflex in humans. This involved injecting dilute ammonia vapour into the subject's breathing system using multiple gas syringes, each filled with a different concentration of ammonia vapour. This chemical stimulus produced temporary closure of the glottis and inhibition of inspiration, sensed by a pneumograph around the subject's waist. The concentration of ammonia required to produce this reflex was 800–1600 p.p.m. Pontoppidan and Beecher [6] investigated the effects of ageing on laryngeal reflexes, using a similar method. Ventilation was monitored with a wet spirometer, but their system contained a considerable deadspace (approximately 300 ml). The results indicated a decrease in protective laryngeal reflexes with increasing age. In 1971, Hinkle and Tantum [7] used a multiple syringe technique with a large deadspace to investigate the effects of codeine phosphate on laryngeal reflexes, and in 1980 Duckett and Hirsh [10] investigated glottic competence in a small number of postoperative patients, and found increased thresholds in all patients who had undergone tracheal intubation.

In 1987, Groves, Rees and Rosen [11] studied the effect of i.v. Diazemuls and lormetazepam on laryngeal reflexes in volunteers. After Diazemuls 15 mg i.v., the ammonia thresholds were increased by 200% and remained increased for more than 4 h.

All of the studies described above suffered from several problems leading to inaccuracy. The final concentration of ammonia reaching the subject's larynx was not known accurately because of large deadspaces [6]. It may also have been affected by streaming or channelling of gas flow through the breathing system; the subjects may therefore have had warning of the imminent arrival of ammonia because the gas was not presented as a bolus. An early prototype of our equipment contained a large deadspace (300 ml), and that was associated with large scatter of results in individual subjects who volunteered that they could sense that the next breath contained ammonia. In further development of our equipment, we have reduced the deadspace volume to 48 ml, with marked improvement in the reproducibility of the results obtained.

The use of pre-prepared syringes and lack of an absorber in these early methods also made them unsuitable for use in the clinical environment.

The mechanism of the glottic stop is not known. Inhalation of irritant vapour stimulates chemoreceptors and rapidly adapting irritant receptors thought to be located in and around the entrance to the larynx. In work by Szereda-Przestaszewska and Widdicombe in cats [12], it was found that the response to insufflation of ammonia vapour across the larynx was virtually abolished by sectioning the superior laryngeal nerve. This provides some evidence for an upper airway site for the afferent limb of this reflex. In earlier work, Widdicombe [13] had observed that mechanical or chemical irritation of the laryngeal mucosa caused laryngeal adduction, even if the stimulus was too weak to cause coughing. It is thought that chemical irritation of the upper airway causes rapid movement of the vocal cords across the inspiratory air flow [7], with interruption to inspiration. With greater inhaled concentrations of irritant vapour, a cough is elicited. A repeatable observation in our subjects was that the glottic stop response occurred at concentrations of ammonia vapour smaller than those required to elicit a cough response.

Previous workers [7], using x-rays to image the movements of the vocal cords, demonstrated that the vocal cords adduct across the inspiratory air flow during a glottic stop, and concluded that this adduction of the vocal cords was the cause of the decrease in the inspiratory air flow. Several of our volunteers spontaneously reported a feeling of sudden involuntary closure in the throat when a glottic stop occurred. Using an ultrasound technique to image the vocal cords [14], we have recorded the movements of the vocal cords during a glottic stop: the cords were seen to adduct rapidly and then abduct, coinciding with the appearance of a glottic stop on the inspiratory flow trace.

In summary, we have described a method of measuring the threshold response of the upper airway to an ammonia stimulus. The subjects found that the technique was acceptable and not unpleasant. Measurements in young, non-smoking volunteers showed a mean threshold of response at ammonia 363–642 p.p.m. There were no significant differences in the mean threshold values recorded on the same day or on separate days.

ACKNOWLEDGEMENTS

We thank Bruel & Kjaer Ltd for the loan of the Multigas analyser. We are also grateful to the Trent Regional Health Authority for a research grant to support the cost of undertaking these studies and to the Association of Anaesthetists of Great Britain and Ireland for an equipment grant.

REFERENCES

1. Burgess GE, Cooper JR, Marino RJ. Laryngeal competence after tracheal extubation. *Anesthesiology* 1979; **51**: 1.
2. Tomlin PJ, Howarth FH, Robinson JS. Postoperative atelectasis and laryngeal incompetence. *Lancet* 1968; **1**: 1402–1405.
3. Siedlecki J, Borowicz JA, Adamski M. Impairment of efficiency of laryngeal defensive reflexes after regaining full consciousness following endotracheal anaesthesia. *Anaesthesia Resuscitation and Intensive Therapy* 1974; **2**: 247–252.
4. Aucott W, Prinsley P, Madden G. Laryngeal anaesthesia with aspiration following intubation. *Anaesthesia* 1989; **44**: 230–231.
5. Hoglund NJ, Michaelsson M. A method for determining cough threshold with some preliminary experiments on the effects of codeine. *Acta Physiologica Scandinavica* 1950; **21**: 168–173.
6. Pontoppidan H, Beecher HK. Progressive loss of protective reflexes in the airway with the advance of age. *Journal of the American Medical Association* 1960; **174**: 2209–2213.
7. Hinkle JE, Tantum KR. A technique for measuring the reactivity of the glottis. *Anesthesiology* 1971; **35**: 634–637.
8. Claeys DW, Lockhart LH, Hinkle JE. The effects of translaryngeal block and Innovar on glottic competence. *Anesthesiology* 1973; **38**: 485–468.
9. Kratschmer F. Uber reflexe von Nasenschleimbaut auf Atmung und kreislauf. *Sitzungsb.d.k.Akad Wein* 1870; **60**: 147–170.
10. Duckett JE, Hirsch RA. Glottic competence in postoperative patients using 2% ammonia. *Anesthesiology* 1980; **53**: S193.
11. Groves ND, Rees JL, Rosen M. Effects of benzodiazepines on laryngeal reflexes. *Anaesthesia* 1987; **42**: 808–814.

12. Szereda-Przestaszewska M, Widdicombe JG. Reflex effects of chemical irritation of the upper airways on the laryngeal lumen in cats. *Respiration Physiology* 1973; **18**: 107–115.
13. Widdicombe JG. Sensory innervation of the lungs and airways. In: Cervero F, Morrison JFB, eds. *Progress in Brain Research*, Vol. 67. Amsterdam: Elsevier Science Publishers B.V., 1986; 49–64.
14. Miles KA. Ultrasound demonstration of vocal cord movements. *British Journal of Radiology* 1989; **62**: 871–872.

British Journal of Anaesthesia 1993; **70**: 131–134

EFFECT OF ORAL DIAZEPAM ON THE SENSITIVITY OF UPPER AIRWAY REFLEXES†

P. J. MURPHY, J. A. LANGTON, P. BARKER AND G. SMITH

SUMMARY

In a double-blind, cross-over study, we have investigated the effect of oral diazepam 20 mg and placebo on the sensitivity of upper airway reflexes in 10 male volunteers (aged 25–35 yr). Upper airway reflex sensitivity (UARS) was assessed using small concentrations of ammonia vapour as a stimulus to upper airway receptors. A threshold concentration of ammonia, at which reflex glottic closure occurred in response to the ammonia stimulus, was used as a measure of UARS. With diazepam, there was significant depression of UARS from 30 to 150 min after administration. (Br. J. Anaesth. 1993; **70**: 131–134)

KEY WORDS

Hypnotics, benzodiazepines: diazepam. Measurement techniques: airway reflexes.

Receptors known to respond to chemical irritants are found in the epithelial and sub-epithelial layers of the larynx and pharynx [1]. Afferents from these fibres travel mainly in the superior laryngeal nerve and synapse in the brain stem. In adult humans, the main responses to irritant receptor stimulation are glottic closure and a brief stop in inspiration [2]. At higher levels of stimulation the reflex response produced is termed the expiration reflex or laryngeal cough (a short expiratory effort without preceding inspiration) [3].

Upper airway reflex activity is important, with implications for both airway protection and upper airway complications during anaesthesia (laryngospasm, coughing). Previous work has shown that subjects given Diazemuls 15 mg i.v. had a 200% decrease in the sensitivity of upper airway reflexes, which persisted for at least 4 h after administration of the drug [4]. The apparent longevity of this reflex depression compared with the short-lived clinical effects of a single dose of i.v. Diazemuls has major implications, as it suggests that a patient may be at increased risk of aspiration despite appearing recovered from acute sedative effects. The aims of this study were to assess the effect of a premedicant dose of oral diazepam on upper airway reflexes and to investigate the time course of this effect.

SUBJECTS AND METHODS

In a double-blind, cross-over study, we have investigated 10 healthy, non-smoking, male volunteers (aged 25–35 yr) who were currently taking no medications. The subjects abstained from alcohol from noon the previous day and had a light breakfast on the day of the study. Exclusions included any subject developing an upper respiratory tract infection within 1 month before or during the study and those with a history of atopy.

Subjects were allocated randomly to receive diazepam 20 mg orally on one occasion, and placebo on another. The investigators and subjects were blinded to the identity of the medication by a system of coded envelopes (the code being broken only at the end of the study).

Baseline measurements of upper airway reflex sensitivity (UARS) and reaction time to an auditory stimulus (ART) were measured, after which subjects ingested the medication. Subsequently, measurements of UARS and ART were made every 30 min for the next 4 h.

At least 1 week later this procedure was repeated, the subject taking the alternative medication.

All subjects were advised not to work or drive a motor vehicle for 24 h after each medication.

Assessment of UARS using small concentrations of ammonia vapour as a chemical stimulus has been described [5–7]. We have recently modified the original technique to produce a more reliable system [8]. UARS was assessed with this new system, as described in the accompanying paper [9].

ART was measured using an electronic timer. We recorded the time taken for the subject to press a trigger in response to an auditory stimulus (bleep) administered via headphones. The bleeps occurred at random intervals. At the end of each 30-min interval, 10 recordings of auditory reaction time were taken and the mean value recorded. Each subject was allowed ample practice time before commencing the study, in order to eliminate practice effects.

Data were analysed using multiple analysis of variance and paired t tests; significance was taken at $P = 0.05$.

After diazepam, paired ART and ammonia threshold values, for each individual at each time-point,

---

This article is accompanied by Editorial I.

P. J. Murphy, F.R.C.ANAES.; J. A. Langton, F.R.C.ANAES.; P. Barker, F.R.C.ANAES.; G. Smith, B.SC., M.D., F.R.C.ANAES.; University Department of Anaesthesia, Leicester Royal Infirmary, Leicester LE1 5WW. Accepted for Publication: August 9, 1992.

†Abstract presented to the Anaesthetic Research Society, Manchester meeting, July 1991.

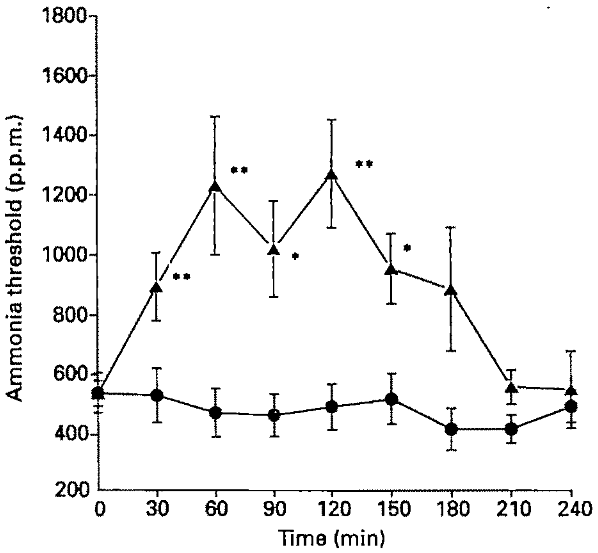


FIG. 1. Relationship between ammonia threshold (mean, SEM) and time. ▲ = Oral diazepam; ● = placebo. $*P < 0.05$; $**P < 0.01$ between groups.

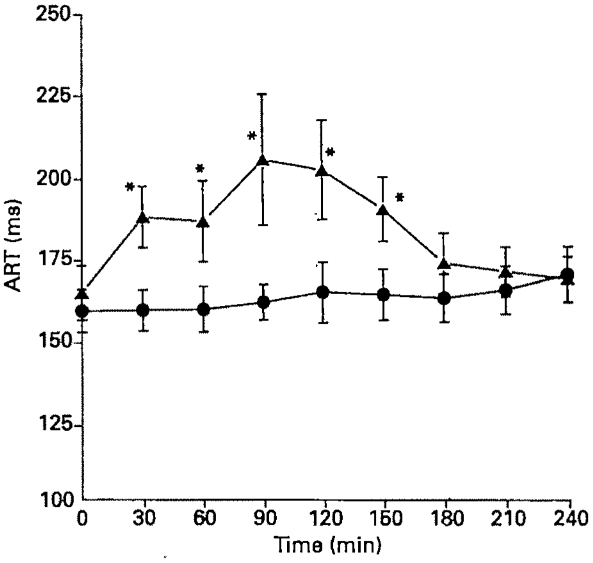


FIG. 2. Relationship between auditory reaction time (ART) (mean, SEM) and time. ▲ = Oral diazepam; ● = placebo. $*P < 0.05$ between groups.

were plotted against each other. Correlation of these variables was tested using the Spearman Rank Correlation Coefficient.

RESULTS

All 10 subjects successfully completed the study. After oral diazepam 20 mg, mean ammonia threshold values increased from a baseline of 538 p.p.m. to a peak of 1266 p.p.m. at 120 min and had decreased to 537 p.p.m. by 240 min. Significant increases in the ammonia threshold concentrations occurred between 30 and 150 min. After placebo there was no significant change in ammonia threshold (fig. 1).

After diazepam, mean ART increased from a baseline of 165 ms to a peak of 205 ms at 90 min and had decreased to 167 ms by 240 min. After placebo, there was no significant change in ART (fig. 2).

Correlation testing of paired ART and ammonia threshold values following diazepam gave an RS value of < 0.2.

DISCUSSION

Ammonia vapour stimulates sensitive nerve endings situated in the laryngeal epithelium and some laryngeal pressure receptors [10]. At a threshold of stimulation, a reflex response occurs which results in glottic closure and a brief pause in inspiration. We have used this ammonia threshold as a measure of upper airway reflex sensitivity.

Simple auditory reaction times have been used before to assess recovery after diazepam [11]. In this study we used ART as a measure of sedation in order to identify the time course of the major sedative effect of oral diazepam.

We have found that, after oral diazepam 20 mg, significant depression of UARS occurred between 30 and 150 min, but within 210 min UARS had returned to baseline values. This change followed a similar time course as changes in ART. However, after diazepam, there was no correlation between individual ART and ammonia threshold values. This lack of correlation may be attributable to several factors. For example, in many individuals the peak effect on ART occurred earlier or later than the peak effect on ammonia threshold. Also, some subjects exhibiting a marked increase in ammonia threshold had only small changes in ART, raising the possibility that measurement of ART may itself lead to increased arousal and in some individuals produce falsely decreased ART values.

After placebo there was no significant change in UARS. These data suggest that there appeared to be little tachyphylaxis to the ammonia stimulus during the period of the study.

The timing of the changes in UARS is explained easily in relation to the pharmacokinetics of oral diazepam. Studies have shown that the mean plasma first-phase half-life of a single oral dose is 5.08 h [12], with the peak effect occurring at 60 min [13, 14]. Although we cannot compare our study directly with one in which i.v. Diazemuls was used, there does appear to be a discrepancy between our results and those of the previous study [4] which demonstrated prolonged depression of UARS with maximal reflex suppression still present at 4 h after Diazemuls 15 mg i.v. Pharmacokinetic data for a single dose of i.v . Diazemuls indicate peak plasma concentrations are achieved within minutes, followed by a rapid decrease in plasma concentrations as redistribution of the drug takes place [13]. Thus one would expect i.v. Diazemuls to have a more transient effect than a similar dose of oral diazepam. This is supported by previous work which suggests that laryngeal competence is impaired for only 5–15 min after i.v. Diazemuls [15].

The answer to this discrepancy may lie in part in the improvement of UARS measurement provided by our new technique. Early work in our department, using a prototype, showed that a large deadspace between the mouthpiece and the switching mechanism resulted in poor reproducibility and an increase in intra-individual variability of UARS measurement. It would appear that a large deadspace alters the presentation of the ammonia stimulus to the laryngeal receptors, presumably by allowing greater mixing of the ammonia stimulus with deadspace gas, such that the rate of increase in the ammonia concentration at the receptor is reduced. As the receptors which respond to the ammonia stimulus are thought to be rapidly adapting [10], it is possible that such changes may result in altered receptor activity. In the previous study, workers used a system with an apparent deadspace of 200 ml. The deadspace in our new system is 48 ml [8].

There was considerable increase in intersubject variability of ammonia threshold values after oral diazepam. It is well known that there is some inter-individual variability in the time taken to reach peak diazepam plasma concentrations after an oral dose. After oral diazepam 0.3 mg kg^{-1}, peak plasma concentrations have been shown to occur within 1 h in more than 80 % of subjects and to have decreased to 30–60 % of maximum values within 6 h in most subjects. However, in some individuals peak plasma concentrations may not occur until 6 h after an oral dose [12].

It is possible also that some of the variability may be secondary to changes in inspiratory flow after diazepam. Studies using citric acid aerosols to induce cough found that slower inspiratory flows were associated with a greater cough stimulus, probably because of increased laryngeal deposition [16]. Although a stimulus technique using ammonia vapour differs from one using a citric acid aerosol, it is possible that changes in inspiratory flow may affect the rate of change of the ammonia stimulus at the laryngeal receptors. Although we used recordings from the pneumotachograph to identify glottic stops, we did not measure inspiratory flow rates accurately. However, previous work has shown that diazepam 0.15 mg kg^{-1} i.v. appears to cause slight, but not significant, depression of mean inspiratory flow rates [17]. It is unlikely, therefore, that any changes in inspiratory flow after oral diazepam would have had a major effect on our measurement of UARS, but they may have added to the variability.

Because the larynx also contains cold receptors and some chemosensitive nerve endings which may not be stimulated by ammonia [10], we cannot be certain that all reflexes evoked by stimulation of laryngeal receptors are depressed to the same extent by diazepam. However, the irritant receptors which respond to ammonia also respond to ether [2] and are most probably implicated in laryngeal reflexes induced by other anaesthetic agents.

The laryngeal closure reflex is thought to be a brainstem reflex and many factors [18], including central inhibitory influences [19], have been shown to affect it. It is probable that diazepam produces suppression of upper airway reflexes by facilitating inhibitory neurotransmitter activity, although it is not clear if this occurs via general depression of CNS activity or via more specific inhibitory pathways.

We conclude that oral diazepam 20 mg resulted in a significant reduction in the sensitivity of upper airway reflexes, as measured by our technique, from 30 to 150 min in healthy young men. This implies that, to depress upper airway reflexes and thus reduce airway complications during induction of anaesthesia, oral diazepam should be administered in the period from 30 min to 2 h before induction. As previous work has shown that upper airway reflex sensitivity decreases with age [20], special care should be taken when using this drug with elderly patients as further depression of upper airway reflexes may be undesirable.

ACKNOWLEDGEMENTS

This study was supported by grants from the Trent Regional Health Authority and the Association of Anaesthetists of Great Britain and Ireland.

REFERENCES

1. Boushey HA, Richardson PS, Widdicombe JG, Wise JCM. The response of laryngeal afferent fibres to mechanical and chemical stimuli. *Journal of Physiology* (London) 1974; **240**: 153–175.
2. Widdicombe JG. Defensive mechanisms of the respiratory system. In: Widdicombe JG, ed. *Respiratory Physiology II*, Vol. 14. Baltimore: University Park Press, 1977; 291–315.
3. Korpas J. Differentiation of the expiration and cough reflex. *Physiologica Bohemoslovaca* 1972; **21**: 677.
4. Groves ND, Rees JL, Rosen M. Effects of benzodiazepines on laryngeal reflexes. *Anaesthesia* 1987; **42**: 808–814.
5. Hoglund NJ, Michaelsson M. A method for determining cough threshold with some preliminary experiments on the effect of codeine. *Acta Physiologica Scandinavica* 1950; **21**: 168–173.
6. Hinckle JE, Tantum KR. A technique for measuring reactivity of the glottis. *Anesthesiology* 1971; **35**: 634–637.
7. Duckett JE, Hirsch RA. Glottic competence in post-operative patients using 2 % ammonia. *Anesthesiology* 1980; **53**: S193.
8. Langton J, Murphy P, Barker P, Smith G. A portable method to assess upper airway reactivity. *British Journal of Anaesthesia* 1991; **67**: 648–649P.
9. Langton JA, Murphy PJ, Barker P, Key A, Smith G. Measurement of the sensitivity of upper airway reflexes. *British Journal of Anaesthesia* 1993; **70**: 126–130.
10. Widdicombe JG. Reflexes from the upper respiratory tract. In: Widdicombe JG, ed. *Handbook of Physiology–The Respiratory System*, Vol. II. Bethseda: American Physiology Society, 1986; 363–394.
11. Gale GD. Recovery from methohexitone, halothane and diazepam. *British Journal of Anaesthesia* 1976; **48**: 691–697.
12. Smith RC, Dekirmenjian H, Davis J, Casper R, Gosenfeld L, Tsai C. Blood level, mood and MHPG responses to diazepam in man. In: Gott LA, Merlis S, eds. *Pharmacokinetics of Psychoactive Drugs: Blood Levels and Clinical Response*. New York: Spectrum Publications Inc., 1976; 141–156.
13. Hillerstad L, Hansen T, Melson H, Privenes A. Diazepam metabolism in normal man, serum concentration and clinical effects after intravenous, intramuscular and oral administration. *Clinical Pharmacology and Therapeutics* 1974; **16**: 479–484.
14. Vickers MD, Schnieden H, Wood-Smith FG. *Drugs in Anaesthetic Practice*. London: Butterworths, 1984; 94–95.
15. Healy TEJ, Vickers MD. Laryngeal competence under diazepam sedation. *Proceedings of the Royal Society of Medicine* 1971; **64**: 85–86.
16. Barros MJ, Zammattio SJ, Rees PJ. The importance of inspiratory flow rate in the cough response to citric acid inhalation in normal subjects. *Clinical Science* 1990; **78**: 521–525.

British Journal of Anaesthesia 1993; 70: 135–140

LOGISTIC REGRESSION ANALYSIS OF FIXED PATIENT FACTORS FOR POSTOPERATIVE SICKNESS: A MODEL FOR RISK ASSESSMENT

M. PALAZZO AND R. EVANS

SUMMARY

One hundred and forty-seven patients undergoing minor orthopaedic surgery were studied prospectively by logistic regression analysis to determine the association of independent fixed patient factors with the incidence of postoperative sickness (nausea, retching or vomiting). Gender, history of previous postoperative sicknness, postoperative opioids and interaction between gender and previous history of sickness were significant independent factors for postoperative sickness; history of motion sickness was weakly associated. The probability of postoperative sickness in the first 24 h after surgery may be estimated from the equation: logit postoperative sickness = $-5.03+2.24$*(postoperative opioids)*$+3.97$*(previous sickness history)*$+2.4$*(gender)*$+0.78$ *(motion sickness)*-3.2*(gender × previous sickness history). (Log likelihood ratio test for 5 degrees of freedom for the coefficients, chi-square = 53.5 (*$P < 0.001$*).) It is suggested that the calculated probability for sickness may be a useful addition for balancing patient treatment groups and allowing between-study comparisons.* (Br. J. Anaesth. 1993; **70**: 135–140)

KEY WORDS
Vomiting: nausea, postoperative, preoperative factors. Risk.

Postoperative sickness (nausea, retching and vomiting) occurs frequently after anaesthesia and surgery. Clinical impressions of a decrease in the incidence and severity of sickness are not supported by evidence published over the past 35 years [1–9] (table I). This may reflect, in part, variability in the method of investigation. There are many alleged causes of postoperative sickness, some patient-related, others technique-related [10, 11]; these factors make adequately controlled clinical trials difficult to conduct. Although most studies control technique factors they usually fail to establish strictly matched patient groups. There may therefore be a need to establish some well-defined criteria by which patients can be considered comparable, particularly for the evaluation of antiemetics. The purpose of this preliminary study was to see if it is possible to provide a basis upon which to define comparable patients.

PATIENTS AND METHODS

Study design

The factors that may influence postoperative sickness may be classified into those related to the patient and those related to anaesthetic technique or management. Patient or technique factors may be classified further as "fixed" or "variable" factors. Fixed factors are those which cannot be altered, such as gender or previous history of sickness. Variable factors are those which may be modified by the anaesthetist. Most patient factors are fixed. In contrast, technique factors may be fixed, or may be allowed to vary depending on experimental design. The primary aim of this study was to isolate and quantify the relative effect of fixed patient factors on the incidence of postoperative sickness. An important aspect of the design of this study, therefore, was to ensure strict control of all possible technique factors while allowing the fixed patient factors to distribute freely without experimental bias among those who vomit and those who do not. Additionally, an attempt was made to reduce the confounding effect of controlled technique factors on the incidence of sickness by using the least emetic anaesthetic technique available. It was hoped that this would highlight the contribution of the fixed factors to postoperative sickness.

The study design and analysis assumed that fixed patient factors did not have equal influences on the incidence of postoperative sickness and, furthermore, that they may have interacted to introduce additional independent variables. For this reason, statistical analysis of individual factor effects was assessed by logistic regression.

Patients

We studied 147 ASA I adult patients (80 female) undergoing minor peripheral orthopaedic surgery,

---

MARK PALAZZO, M.B., CH.B., M.R.C.P., F.R.C.ANAES., M.D., Department of Anaesthetics, Charing Cross Hospital, Fulham Palace Road, London W6. RHYS EVANS, B.SC., M.B., B.S., F.R.C.ANAES., D.PHIL., Nuffield Department of Anaesthetics, Oxford. Accepted for Publication: September 4, 1992.

Correspondence to M.P.

TABLE I. *Some previous studies examining postoperative sickness: nausea (N), retching (R) or vomiting (V) included in the study. *Retrospective study. NA = Not available*

Reference	Sample size	Gender of subjects	Sickness (%)	Observation period (h)	NVR
[9] (1936)*	10000	M/F	40.6	NA	NV
[2] (1955)	3000	M/F	27.2	24	VR
[1] (1957)	1702	M/F	32.0	24–36	NV
[3] (1958)	1561	M/F	30.5	24	NVR
[4] (1960)	748	M/F	19.4	2.5	NV
[5] (1961)	2230	M/F	23.0	6.0	RV
[7] (1970)	110	F	30.9	24	NV
[6] (1979)	40	F	55.0	24	NVR
[8] (1982)	96	F	34.4	24	NVR

TABLE II. *Some of the factors that may be associated with postoperative sickness. These can be classified into factors associated with the patient or those associated with technique. Most patient factors are fixed. Variable factors, either patient or technique may be fixed by study design*

Factors examined	Factors controlled
Age	Preoperative assessment
Weight	Premedication
Sex	Induction agent
Duration of preoperative fast	Maintenance agents
Previous postoperative emetic history	Oropharyngeal suction
History of motion sickness	Guedel airway
History of sickness with pregnancy	Mask ventilation
Heartburn	I.v. fluids
History of sickness with pain	Journey to theatre from ward
History of sickness with alcohol	Journey from theatre to recovery
Anxiety before induction	Recovery position
Nausea before induction	Duration of postoperative observation
Thirst before induction	Nurses observing patients
Hunger before induction	Anaesthetist
Duration of anaesthesia	Time of first ambulation
Opioid administration	Time to first oral intake

presenting sequentially over a 3-year period. Patients who were pregnant or lactating were not included. Hospital Ethics Committee approval and patient agreement to the study were obtained before the study. In order not to alert patients to our special interest in postoperative sickness, their consent was sought for the investigation of a variety of postoperative complications.

All patients were admitted to the same ward the evening before surgery. Each patient was interviewed by one of the investigators as part of the routine preoperative assessment. A standard questionnaire was used to determine the fixed factors from the patient's history. Questions were distributed equally between those which were thought relevant to postoperative sickness and those which were not; the questions were asked in random order, to minimize bias.

Patients were allocated randomly to receive either a light meal or no meal 6 h before anaesthesia. All patients received oral premedication with diazepam 10 mg 90 min before anaesthesia. Patients, lying supine, were taken by trolley from the ward to the anaesthetic room, so that all experienced the same journey.

In the anaesthetic room, the patients were asked additional questions which sought information on whether or not the patient was hungry, thirsty, sleepy, anxious or feeling sick before induction of anaesthesia.

Anaesthesia was induced with thiopentone 4 mg kg^{-1}, followed by oxygen 3 litre min^{-1}, nitrous oxide 6 litre min^{-1} and increasing concentrations of enflurane via a Bain system. Care was taken to avoid apnoea, thus obviating the need for ventilatory assistance by mask. During induction, insertion of a Guedel airway and oropharyngeal suction were avoided. Patients who had ventilatory assistance, suction or insertion of an oropharyngeal airway at any time during the anaesthetic management were excluded from the analysis. No patient received supplementary local or regional anaesthesia.

Anaesthesia was maintained by spontaneous ventilation of a mixture of 2% enflurane and 65% nitrous oxide in oxygen via a face mask and Bain system. Patients were monitored with non-invasive arterial pressure measurements, pulse oximetry and ECG.

All patients received an i.v. infusion of Hartmann's solution during anaesthesia. The volume administered was calculated to compensate for the period of fasting and included any additional loss during surgery. The infusion was completed before the end of surgery. The volume for the fasting period was calculated as 1.5 ml kg^{-1} h—for example, a 70-kg patient who had fasted for 7 h received 735 ml.

At the end of anaesthesia, a standard routine was followed for each patient. All patients were placed in the left lateral position, received supplementary oxygen therapy and were sent to a 24-h recovery room with attention paid to the airway, avoiding oropharyngeal suction or insertion of a Guedel airway. If there was a need for additional airway intervention at this stage, the patient was withdrawn from the study. A total of 11 patients were excluded, for reasons of loss of postoperative data (six patients), variation from the study design (four patients) and inadvertent inclusion of one patient twice.

Patients were allowed papaveretum, paracetamol and antiemetics as required. Consequently, postoperative opioid analgesia was considered a fixed factor for the purposes of this study and was not controlled. The total dose of analgesics administered was recorded over 24 h. All episodes of postoperative sickness were recorded for 24 h. Postoperative sickness was defined as vomiting (an integrated reflex which results in forceful expulsion of stomach contents), retching (a non-productive vomit) and nausea (the sensation of wishing to vomit or retch). No attempt was made to grade the severity of postoperative sickness. A "vomiter" was any patient who had at least one episode of nausea, retching or vomiting. Episodes of nausea, retching and vomiting were either volunteered, witnessed or elicited as the result of direct questioning by the nursing staff. Concomitant changes in heart rate, arterial pressure and ventilatory frequency were recorded with any obvious provocative episodes such as early ambulation. Oral fluids were not given until 4 h after anaesthesia, but were freely available thereafter. The same nurses observed all the patients (maximum four patients cared for by one recovery nurse) throughout the study. These nurses were aware of a study on postoperative complications but were not aware of its design or of the patients' responses to previous questioning. Table II shows a list of all the factors that were examined.

Statistical analysis

The data obtained from this study were either categorical, such as patient gender, or continuous, such as age, weight and duration of anaesthetic. The anaesthetic technique factors were strictly controlled, leaving the patient factors to distribute freely.

All the continuous data were examined by Mann–Whitney *U* test between vomiters and non-vomiters. Significant statistical differences were assumed at $P < 0.05$. All the categorical data that were not controlled by study design (fixed patient factors) were also examined initially by a univariate method (2×2 contingency tables) between vomiters and non-vomiters for rapid identification of possible important differences. The uncontrolled categorical data (fixed patient factors) and continuous data (age, weight, duration of fast and duration of operation) were examined by logistic regression (logit module, Systat 5.1 for the Macintosh, Systat, Illinois, U.S.A.). Logistic regression makes no assumption about distribution.

The independent factors were indicated as 1 if present and 0 if absent (for gender 1 was female and 0 male). The inclusion of factors was determined by a forward stepwise regression of the main factors, followed by interactions. The threshold for inclusion of a factor was a probability of 0.15 or less based on log likelihood test ratio $G(G = -2$ (log likelihood test ratio for the model without the additional factor) – (log likelihood test ratio for the model with the additional factor)) [12].

Maximum likelihood estimators (coefficients) were calculated for each factor from which odds ratios were determined. The odds ratios were expressed as probabilities for postoperative sickness. The probabilities of postoperative sickness for baseline and various factor combinations were calculated with their 95% confidence limits [12, 13].

Examples of these calculations are shown in the Appendix.

RESULTS

The uncontrolled factors (continuous and categorical) examined are listed in table II. The continuous variables, age, weight, duration of operation and duration of fast were distributed evenly between vomiters and non-vomiters (table III). These factors also failed to reach the inclusion criteria for the logistic regression model. Their coefficients were less than 0.01 and log likelihood test ratios gave *P* values between 0.4 and 0.6.

The uncontrolled categorical factors (fixed patient factors) were also analysed initially by 2×2 contingency tables between vomiters and non-vomiters (table IV). Among these factors, only four appeared to have any association with the incidence of postoperative sickness when examined by univariate analysis: patient gender, a previous history of postoperative sickness, postoperative opioid analgesics, and a history of motion sickness (table IV). When forward stepwise logistic regression analysis was applied to the uncontrolled categorical data, the following independent factors met the criteria for inclusion in the model for postoperative sickness: postoperative opioid analgesia, gender, previous history of postoperative sickness, motion sickness and an independent interaction between gender and previous sickness history (table V). Motion sickness had the weakest association and unlike the other factors did not reach statistical significance at the 0.05 level, possibly because of low power, estimated at 0.65. Assuming the same trend in the distribution of motion sickness among vomiters and non-vomiters, 800 patients would have been required to reach statistical significance.

The relative effects of these factors may be summarized by the logistic regression equation: $\text{Log}_e(p/1-p)$—that is:

$$\begin{aligned}&\text{Logit postoperative sickness} = -5.03 + 2.24\\&(\text{postoperative opioids}) + 3.97(\text{previous sickness}\\&\text{history}) + 2.4(\text{gender}) + 0.78(\text{history of motion}\\&\text{sickness}) - 3.2(\text{gender} \times \text{previous sickness history})\end{aligned}$$

where p = proportion of patients with sickness and $1-p$ = proportion without sickness. The presence of postoperative opioids, previous sickness history, female gender, and history of motion sickness are coded as 1 in the model; absence of these factors is coded as 0.

TABLE III. *Patient data (median (range)) for vomiters and non-vomiters. No significant differences within gender groups*

	Males		Females	
	Vomiters	Non-vomiters	Vomiters	Non-vomiters
Age (yr)	41 (18–63)	36 (16–78)	50 (14–72)	53 (15–77)
Wt (kg)	75 (66–86)	76 (54–128)	62 (41–98)	65 (45–82)
Duration of operation (min)	35 (30–60)	47.5 (17–115)	42 (10–73)	36 (20–115)
Duration of fast (min)	660 (370–780)	540 (320–830)	620 (380–990)	715 (380–980)
Total No. patients	9	58	31	49

TABLE IV. *Univariate analysis of the categorical data*

	Vomiter (No.)	Non-vomiter (No.)	Vomiter (%)	Non-vomiter (%)	P
Opioid analgesic (papaveretum) 24 h postop.	36	56	39.1	60.9	0.0001
No opioid analgesic (papaveretum) 24 h postop.	4	51	7.3	92.7	
Previous history of PNVR	21	22	48.8	51.2	0.0003
No previous history of PNVR	19	85	18.3	81.7	
Males	9	58	13.4	86.6	0.0012
Females	31	49	38.7	61.3	
Morning sickness	18	23	43.9	56.1	0.7
No morning sickness	9	16	36.0	64.0	
History of motion sickness	10	14	41.7	58.3	0.13
No history of motion sickness	30	93	24.4	75.6	
Breakfast	8	24	25.0	75.0	0.9
Overnight fast, no breakfast	32	82	28.1	71.9	
Suffer with heartburn	12	22	35.3	64.7	0.3
No heartburn	28	85	24.8	75.2	
Nervous at time of induction	15	35	30.0	70.0	0.7
Not nervous at time of induction	25	72	25.8	74.2	
Hungry at time of induction	22	51	30.1	69.9	0.5
Not hungry at time of induction	18	56	24.3	75.7	
Thirst at time of induction	22	60	26.8	73.2	0.9
No thirst at time of induction	18	47	27.7	72.3	
Nausea in anaesthetic room before induction	3	3	50.0	50.0	0.4
No nausea in anaesthetic room before induction	37	104	26.2	73.8	
Antiemetics postop.	34	0	100	0	0.0001
No antiemetics postop.	6	107	5.3	94.7	
Alcohol does not normally make feel sick	32	94	25.4	74.6	0.28
Alcohol normally makes feel sick	6	8	42.9	57.1	
Pain does not normally make feel sick	39	102	27.7	72.3	0.9
Pain normally makes feel sick	1	5	16.7	83.3	

TABLE V. *Logistic regression analysis of factors associated with postoperative sickness during the first 24 h after orthopaedic surgery (peripheral limb surgery). The overall odds ratio for emesis is given by the solution to: logit postoperative sickness* $= -5.03 + 2.24$*(postoperative opioids)* $+ 3.97$*(previous sickness history)* $+ 2.4$*(gender)* $+ 0.78$*(history of motion sickness)* $- 3.2$*(gender × previous sickness history) where* -5.03 *is the constant. The presence of opioids, previous sickness history, motion sickness and female gender are coded as 1 in the above equation; absence of these factors or male gender is coded as 0*

Independent factors influencing postoperative sickness	Coefficient x	SE (coeff.)	Odds ratio e^x	95% CI (odds ratio)	P
Constant	−5.03	0.92	0.01	0.001–0.039	< 0.001
Postoperative opioids	2.24	0.62	9.39	2.77–31.82	< 0.001
Previous history of sickness after anaesthesia	3.97	1.03	52.98	7.01–403.0	< 0.001
Effect of gender	2.4	0.79	11.02	2.34–51.94	< 0.005
History of motion sickness	0.78	0.57	2.18	0.71–6.68	$< 0.2 > 0.1$
Interaction of gender × previous sickness history	−3.20	1.14	0.04	0.0043–0.37	< 0.01

The log likelihood ratio test for the model produced a chi-square value of 53.5, $P < 0.001$ (5 degrees of freedom).

The most surprising finding was that, although males have an intrinsically lower probability of postoperative sickness than females, the effect of a previous history of sickness in a male increases the risk to greater than that for females (table VI).

TABLE VI. *List of probability calculations for postoperative sickness depending on the combination of independent fixed patient factors. Baseline probability represents a male with no previous history of sickness or motion sickness who did not receive opioid analgesics. Baseline odds ratio for postoperative sickness is the solution to* e^x *where* $x = -5.03$. *The odds ratios* (OR), *0.01, may be converted to a probability from* $P = OR/1 + OR$,*—that is* $P = 0.01/1.01$ = *approximately 1% probability for postoperative sickness*

Combination of independent factors influencing postoperative sickness	Probability of postop. sickness (%)	95% CI of the probability of postop. sickness
Males	1	0.1–3.8
Males with a history of motion sickness	1	0.2–9.0
Males receiving postop. opioids	5.6	2.0–25.0
Females	6.7	2.0–20.0
Males with a history of motion sickness receiving postoperative opioids	11.5	1.9–45.0
Females with a history of previous sickness	13.5	0.4–85.0
Females with a history of motion sickness	13.8	2.9–43.0
Females with previous sickness and history of motion sickness	25.1	0.9–87.0
Males with a previous history of sickness	25.7	6.5–64.0
Females receiving postoperative opioids	40.3	26.0–56.0
Males with a previous history of sickness and motion sickness	43.0	9.9–83.0
Females with previous history of sickness receiving postoperative opioids	59.3	15.9–93.0
Females with history of motion sickness receiving postoperative opioids	59.5	28.5–84.2
Females with a previous history of sickness and motion sickness receiving opioids	76.1	20.0–97.0
Males with previous history of sickness receiving opioids	76.4	49.0–91.0
Males with a previous history of sickness and motion sickness receiving opioids	87.6	53.0–97.0

DISCUSSION

Progress in identifying important factors for postoperative sickness may have become confounded by methodology that does not take account of fixed patient factors or their distribution, thereby introducing sample bias. The majority of studies have evaluated the merits of antiemetics in groups usually matched only by gender and anaesthetic technique. Further progress in the prevention of sickness may be facilitated if some method is adopted for assessing the inadvertent bias resulting from patient factors. The method we propose, based on logistic regression analysis, allows individual patient probability for postoperative sickness and the mean probability for a heterogenous group of patients to be calculated. The mean probability for sickness for groups of patients provides an additional comparison for within and between studies by examining the predicted and observed vomiting rates. Similar calculations might be preferable to historical controls for single group studies whereas, for very large studies, patients with similar probabilities may be risk-stratified into homogenous groups.

Commonly, groups of patients with many influencing factors are described as "balanced" if the frequency of factors is the same in each study group. This can be conveniently described as global balancing. However, it would appear to be inappropriate to apply global balancing to groups made up of heterogenous patients if the probabilities for sickness caused by the factors are different and logarithmically related. This is the case for probabilities derived by logistic regression. This may be illustrated by an example. Consider two groups of 10 patients, each group has five women and five men; in addition, five of these patients (males, females or both) in each group have a previous history of sickness. These two groups would be globally balanced. However, using our own model, they would not be balanced by risk if, in one group, the previous history of sickness was only present in the five males whereas, in the other group, previous history of sickness was associated with the five females. The mean probability of sickness for the group in which previous sickness is associated with males would be 16.2% whereas, in the group where it is associated with females, the mean probability for the group would be 7.25.

This study has identified previous history of postoperative sickness, female gender, history of motion sickness, an interaction between gender and previous history and postoperative opioids as fixed patient risk factors. Postoperative opioid administration was included as a fixed factor: for ethical reasons it was not controlled, and therefore it distributed according to patient requirement. There is a practical difficulty in deciding if sickness in patients who have received opioids is caused by pain, or opioids, or if it would have occurred irrespective of these two factors. Even if sickness always occurred after administration of opioids, it is still difficult to decide the time that has to elapse before a bout of sickness can be ascribed to another cause. In this study, the analysis has shown an association between sickness and receipt of opioids at some time during a 24-h period. Fortunately, 55 patients did not receive opioids by choice, and this provided a control group. Therefore it is possible to be more confident of opioids as a cause of sickness.

A criticism of this study may be the small sample from which coefficients were derived for the model. This decreases the power of the study and produces wide confidence limits, in particular when several factors are combined. We attempted to reduce our requirements for large numbers and yet maintain power by strict control of anaesthetic technique. Additionally, a surgical procedure and anaesthetic method were chosen in which the potential for confounding emetic effects related to these procedures was kept to a minimum. In spite of the small numbers, the model obtained highly significant effects from postoperative opioids, gender, previous emetic history and the interaction between gender and previous emetic history. Motion sickness failed to reach statistical significance at 0.05, possibly because of low power (0.65), but met the standard inclusion criteria for the model suggested by Hosmer and Lemeshow [12]. The reason for the lack of power could, in part, be ascribed to the study design, which allowed opioids to be administered only after the journey to the 24-h observation area; the suggested vestibular sensitization by opioids may therefore have been averted [14]. Alternatively, the effect of motion sickness may be small when compared with other factors.

The proposed model can only be considered useful if, when tested prospectively with patients other than those used in the study, it produces high correct classification rates for vomiters and non-vomiters. Therefore the statistical techniques of bootstrapping or jack-knifing which use the original data set to evaluate the ability of the model to classify patients correctly were not used. In evaluating the model, it should be noted that this study was limited to peripheral orthopaedic surgery and therefore the derived coefficients for fixed factors may need to be interpreted with caution when the model is applied to types of surgery having strong associations with postoperative sickness.

APPENDIX

The solution to the equation: $\text{Log}_e\,(p/1-p)$—that is:

Logit postoperative sickness $= -5.03 + 2.24$ (postoperative opioids) $+ 3.97$(previous sickness history) $+ 2.4$(gender) $+ 0.78$(history of motion sickness) $- 3.2$(gender × previous sickness history)

(where p = proportion of patients with sickness; $1-p$ = proportion without sickness; presence of postoperative opioids, previous sickness history, female gender, and history of motion sickness are coded as 1 in the model, absence of these factors coded as 0)

provides the basis for calculating the probability of sickness within 24 h in any particular patient.

For calculating the risk of any group of patients, the individual patient probabilities should be summed and divided by the number of patients, to provide a mean value and SD.

Calculation of individual risks is shown in examples 1 and 2.

Example 1

Baseline probability of sickness is calculated with all independent variables coded as 0:

$$\text{Logit postoperative sickness} = \text{constant} = -5.03$$

From this the odds ratio can be calculated:

$$\text{Odds ratio} = e^{-5.03} = 0.01$$

(The solution to e^x where $x = -5.03$ may be found in exponential tables.)

Derivation of the probability (P) of sickness from the odds ratio is given by:

$$P = \text{odds ratio}/1 + \text{odds ratio}$$

In the above example, P is approximately 0.01 or 1%.

Example 2

Male with a previous history of sickness and motion sickness who also received opioids.

Logit postoperative sickness

$$= -5.03 + 2.24(1) + 3.97(1) + 2.4(0) + 0.78(1) - 3.2(0 \times 1)$$
$$= -5.03 + 2.24 + 3.97 + 0.78$$
$$= 1.96$$
$$e^{1.96} = 7.09$$

probability of sickness in 24 h

$$= 7.09/8.09 = 0.876 \text{ or } 87.6\%$$

The 95% confidence limits for the probability of sickness was derived from the coefficient estimate $\pm 1.96\sqrt{\text{variance}}$ of the coefficient estimate. The upper and lower coefficient estimates thus calculated were converted to odds ratios using exponential tables, which in turn were used to calculate the 95% confidence limits for the probability of sickness.

The variance for a combination of risk factors is calculated from the sum of the independent factor estimate variances plus twice the covariances of the combined independent factor estimates. The 95% confidence limits for the probability of sickness for various independent factors are shown in table VI.

REFERENCES

1. Burtles R, Peckett BW. Postoperative vomiting. *British Journal of Anaesthesia* 1957; **29**: 114–123.
2. Dent S, Ramachandra V, Stephen CR. Postoperative vomiting; incidence analysis and therapeutic measures in 3000 patients. *Anesthesiology* 1955; **16**: 564–572.
3. Bonica JJ, Crepps W, Monk B, Bennett B. Postoperative nausea, retching and vomiting. *Anesthesiology* 1958; **19**: 532–540.
4. Bellville JW, Bross IDJ, Howlands WS. Postoperative nausea and vomiting. IV, Factors related to postoperative nausea and vomiting. *Anesthesiology* 1960; **21**: 186–193.
5. Adriani J, Summers FW, Anthony SO. Is the prophylactic use of antiemetics in surgical patients justified? *Journal of the American Medical Association* 1961; **175**: 666–671.
6. Korttila, K, Kauste A, Auvinen J. Comparison of domperidone, droperidol, and metoclopramide in the prevention and treatment of nausea and vomiting after balanced general anesthesia. *Anesthesia and Analgesia* 1979; **58**: 396–400.
7. McKie BD. Postoperative nausea and vomiting: A review of their incidence, causes and effects. *Australian and New Zealand Journal of Surgery* 1970; **39**: 311–314.
8. Mortensen PT. Droperidol postoperative antiemetic effect when given intravenously to gynaecological patients. *Acta Anaesthesiologica Scandinavica* 1982; **26**: 48–52.
9. Waters RM. The present state of cyclopropane. *British Medical Journal* 1936; **2**: 1013–1017.
10. Palazzo MGA, Strunin L. Anaesthesia and emesis I. Etiology. *Canadian Society of Anaesthetists Journal* 1984; **31**: 178–187.
11. Watcha M, White P. Postoperative nausea and vomiting. Its etiology, treatment and prevention. *Anesthesiology* 1992; **77**: 162–184.
12. Hosmer D, Lemeshow S. *Applied Logistic Regression.* Chichester: John Wiley and Sons, 1989.
13. Altman D. *Practical Statistics for Medical Research.* London: Chapman and Hall, 1991.
14. Comroe J, Dripps, R. Reactions to morphine in ambulatory and bed patients. *Surgery, Gynecology and Obstetrics* 1948; **87**: 221–224.

British Journal of Anaesthesia 1993; 70: 141–144

COMPARISON OF AUTOMATIC OSCILLOMETRIC ARTERIAL PRESSURE MEASUREMENT WITH CONVENTIONAL AUSCULTATORY MEASUREMENT IN THE LABOUR WARD

M. A. HASAN, T. A. THOMAS AND C. PRYS-ROBERTS

SUMMARY

We have compared two non-invasive methods of arterial pressure (AP) measurement used in labour wards: an automatic oscillometric measurement obtained by Dinamap 1846, and a conventional auscultatory measurement obtained by midwives. A total of 369 AP measurements were recorded, involving 28 normotensive and hypertensive pregnant women during labour, with or without extradural analgesia. Compared with the midwife group, the Dinamap group had a greater systolic AP, by 2.7 mm Hg ($P < 0.01$) and smaller diastolic AP, by 9.8 mm Hg ($P < 0.01$). The correlations between the two methods were highly significant, but the limits of agreement were relatively wide for both systolic and diastolic AP measurements. We conclude that a clinically important difference exists in diastolic AP measurements. Dinamap diastolic AP must be corrected using a regression equation, or simply by adding 10 mm Hg, before being compared with the available normal and hypertensive AP values. (Br. J. Anaesth. 1993; **70**: 141–144).

KEY WORDS

Arterial pressure: measurement. Equipment: manometers. Pregnancy.

Many studies have correlated the accuracy and consistency of automatic oscillometric devices with indirect auscultatory measurements [1, 2], and direct intra-arterial pressure measurements [3–9] in general adult populations [1, 3, 7], neonates [5, 6], children [2], cardiac [4, 5, 9] and critically ill patients [6, 8]. So far, studies on women in labour have not been published. A preliminary report was mentioned in a published letter [10].

Arterial pressures in labour wards are normally measured by midwives using sphygmomanometry with auscultation of phases 1 and 4 of the Korotkoff sounds to identify systolic and diastolic pressures, respectively. Published normal AP values in obstetric patients have been measured in this way. The definition, classification and subsequent treatment strategies of hypertensive disorders of pregnancy depend on pressures measured in this manner. Diastolic pressure has traditionally been the main diagnostic and prognostic indicator in obstetric patients [11] and is taken as the point of muffling (phase 4 of Korotkoff sounds) [12]—a reading which may not correspond or correlate with the true intra-arterial pressure [9] or the diastolic reading on the Dinamap 845 [1].

The introduction of automatic oscillometric measurement in labour wards should be accompanied by a knowledge of its performance in obstetric patients. Direct comparison with published (auscultatory) data may be misleading. Compensation for differences between oscillometric and auscultatory measurements concluded from studies in non-pregnant patients may not be applicable. Therefore, we have aimed to define the relation between the two measurements to enable the interpretation of oscillometric measurements in the light of available published data.

PATIENTS AND METHODS

Twenty-eight pregnant women admitted to the Central Delivery Suite at the Bristol Maternity Hospital were selected randomly for participation in the study, which was approved by the District Ethics Committee; each patient's verbal consent was obtained. The two methods studied were: Dinamap (D) measurement, an automatic oscillometric AP measurement using Dinamap 1846 (Critikon Ltd) operated by the investigator (M.A.H.); and midwife (M) measurement, a conventional auscultatory measurement taken by midwives using mercury sphygmomanometry and auscultation (Korotkoff sounds phases 1 and 4 to identify systolic and diastolic AP, respectively). No special arrangement was introduced in the selection of midwives, who were those normally involved in AP measurements in the labour ward.

Modification of sphygmomanometer tubing with the introduction of two-way stopcocks allowed the use of a single standard adult AP cuff (bladder dimensions 13×23 cm) for all the measurements with the Dinamap or sphygmomanometer. The patient's arm circumference was recorded. The Dinamap was calibrated before and at intervals throughout the study.

M. A. HASAN, M.B., CH.B., D.A., F.R.C.ANAES.; C. PRYS-ROBERTS, M.A., D.M., PH.D., F.R.C.ANAES., F.F.A.R.A.C.S; Sir Humphry Davy Department of Anaesthesia, University of Bristol, Bristol Royal Infirmary, Bristol BS2 8HW. T. A. THOMAS, M.B., CH.B., F.R.C.ANAES., Department of Anaesthesia, Bristol Maternity Hospital, Southwell Street, Bristol BS2 8EG. Accepted for Publication: August 21, 1992.

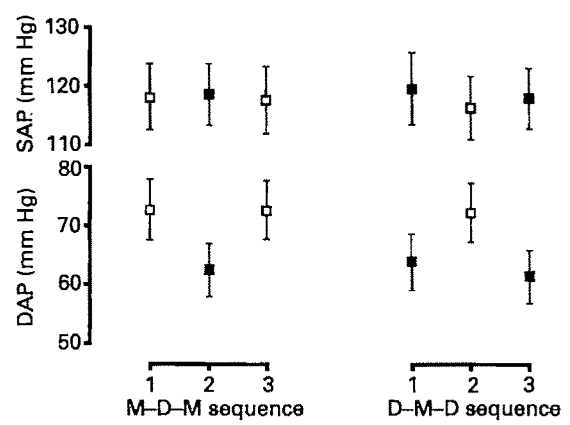


FIG. 1. Midwife (□) and Dinamap (■) measurements of systolic (SAP) and diastolic (DAP) arterial pressures taken in the order midwife–Dinamap–midwife (M–D–M) or Dinamap–midwife–Dinamap (D–M–D) (mean, 95 % confidence interval).

All AP comparisons were performed in sets of three successive measurements, comparison midwife–Dinamap–midwife (M–D–M) sequence (odd numbered sets) or Dinamap–midwife–Dinamap (D–M–D) sequence (even numbered sets). These measurement sets were repeated every 15–30 min, avoiding periods of haemodynamic instability, such as during a uterine contraction or after the injection of extradural local anaesthetic. Patients were maintained in a lateral tilt (approximately 30°) position for 5 min before and during each set of measurements, with the arm AP cuff always kept at the level of the heart. These comparison sets were repeated on up to 10 occasions for each patient. More than one midwife was allowed to make measurements in any individual patient.

Throughout the measurements, special care was taken to ensure that both the midwife and the investigator were blind to each other's recordings, which were kept separate until the measurements were completed.

Results were analysed by Minitab statistical software (version 7.2) using an IBM compatible 386 PC. Tests included: one-way analysis of variance (one factor); two-way analysis of variance (two factors), paired Student's t test, correlation and regression analyses. Limits of agreement were analysed according to Bland and Altman [13]. Probabilities of less than 0.05 were considered to be significant.

RESULTS

We studied 28 pregnant women aged 19–36 yr. Their gestations were 36–42 weeks. All were in the first stage of labour at the time of study. Their arm circumferences were 21–38 cm. Five women had auscultatory diastolic AP recorded at 90 mm Hg or greater on two or more occasions during their antenatal care. Four of these five women also had proteinuria. Seven women received extradural analgesia during part or all the period of observations.

A total of 123 comparison sets were performed (average of 4.4; range 3–9 sets per patient). Fourteen midwives participated in the study (range 1–3 midwives per patient). There were no failures of measurement with either of the two methods.

Results of AP measurements for both the M–D–M sequence and the D–M–D sequence are presented as mean and 95 % confidence intervals (fig. 1). Two-way analysis of variance of AP measurements using two factors, time (first, second, or third measurement), and method (midwife or Dinamap) showed a significant difference in the method of diastolic AP measurement. Paired Student's t tests showed significant differences between the two methods in diastolic AP measurement in the M–D–M sequence, and in systolic and diastolic AP measurements in the D–M–D sequence. Average difference (midwife minus Dinamap measurements) were -2.7 and 9.8 mm Hg for systolic and diastolic AP, respectively ($P < 0.01$).

Correlations between measurements from the two methods were $r = 0.85$ and $r = 0.834$ with regression equations of $[\mathrm{M} = 11.3 + 0.883 \times \mathrm{D}]$ and $[\mathrm{M} = 9.83 + 1.01 \times \mathrm{D}]$ for systolic and diastolic measurements, respectively ($P < 0.01$).

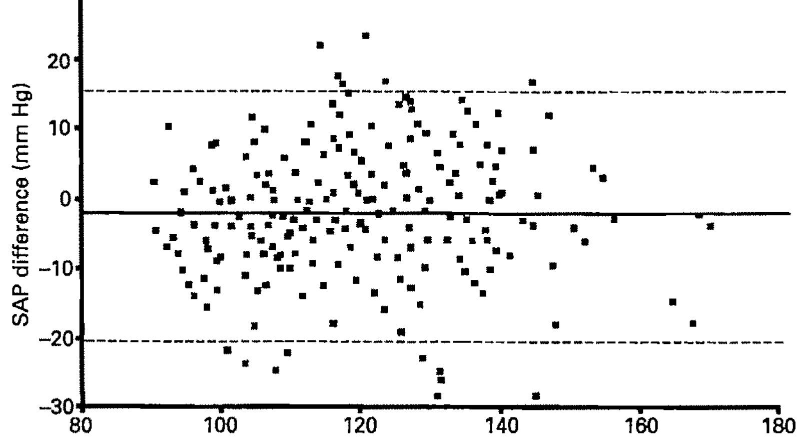


FIG. 2. Systolic arterial pressure (SAP) differences between midwife and Dinamap measurements (M−D), against average SAP of midwife and Dinamap measurements ((M+D)/2). —— = Mean of differences; ---- = limits of agreement (mean, 2 SD).

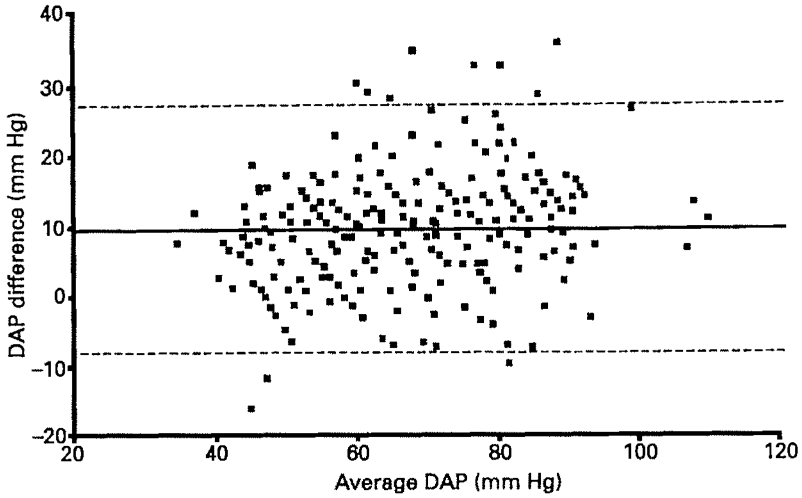


FIG. 3. Diastolic arterial pressure (DAP) differences between midwife and Dinamap measurements (M−D), against average DAP of midwife and Dinamap measurements ((M+D)/2). —— = Mean of differences; ---- = limits of agreement (mean, 2 SD).

According to the method of Bland and Altman, AP differences between the two methods were plotted against the average of both for systolic and diastolic AP, respectively (figs 2, 3). Limits of agreement between the two methods (mean (2 SD) of the difference (M minus D)) were −20.7 to +15.3 mm Hg for systolic, and −7.6 to +27.3 mm Hg for diastolic AP measurements (represented by the dotted horizontal lines). The mean differences (−2.7 mm Hg and 9.8 mm Hg for systolic and diastolic AP measurements, respectively) are represented by continuous lines. The scatter of points in figures 2 and 3 indicates lack of a change in magnitude of differences between the two methods with a change in the value of systolic or diastolic AP, respectively.

Dinamap diastolic AP measurements failed to identify auscultatory diastolic values of 90 mm Hg or greater (a threshold normally taken for close observation of AP) and 110 mm Hg or greater (a threshold taken for urgent therapeutic intervention) in 40 of 47, and in all of eight occasions, respectively. When Dinamap measurements were corrected (by adding 10 mm Hg), only 23 of 47 and four of eight such occasions failed to be identified, respectively. However, corrected Dinamap measurements identified (incorrectly) diastolic values of 90 mm Hg or greater on five occasions when auscultatory diastolic values were less than 90 mm Hg. There were no corrected Dinamap diastolic values at or greater than 110 mm Hg when corresponding auscultatory values were less than 110 mm Hg.

There were no relationships between arm circumference and systolic or diastolic AP differences between the two methods.

DISCUSSION

Our results have shown that a statistically significant and clinically important difference exists in the diastolic AP measurement between the two methods. This diastolic difference was irrespective of the order of measurements (M–D–M or D–M–D in figure 1) or the value of diastolic AP (lack of the relationship between diastolic AP difference and average diastolic AP in figure 3).

The finding of a large diastolic difference (almost 10 mm Hg) is broadly consistent with that of a recent preliminary report [10], but contrasts with results obtained from non-pregnant patients in whom Dinamap diastolic measurements were 3–4 mm Hg smaller than phase 4 auscultatory diastolic measurements [1]. This may be related to diastolic phase 4–5 discrepancy. In pregnancy, haemodynamic changes such as increased cardiac output and decreased systemic vascular resistance may affect this discrepancy. A large survey has shown, in many pregnant women, large gaps between phases 4 and 5 and sometimes very small values (reaching zero) in phase 5 [14]. The large diastolic difference in our study may be explained by the fact that midwives measure phase 4, while Dinamap diastolic measurement correlates with phase 5 diastolic AP measurement [1]. It would be interesting, but difficult, to speculate on how these two measurements would relate to direct intra-arterial measurements. Such relationships have not been studied in pregnant women and relevance of studies from non-pregnant patients is questionable.

High correlations between the two methods are not surprising, as the two methods are designed to measure the same variable. The wide limits of agreement between the two methods, shown in figures 2 and 3, reveal a considerable degree of variability which may be the result of the combined variabilities from two methods of indirect AP measurement. Repeatability of Dinamap or same midwife measurements were good. Repeated Dinamap measurements in figure 1 were not significantly different. Repeated measurements for the same midwife were almost identical (fig. 1); these may have been biased by awareness by the midwife of her initial measurement. Repeatability of measurements between different midwives was difficult to test, as different midwives were usually involved in measurements from different patients.

We conclude that Dinamap diastolic AP (if uncorrected) may be misleading when compared with the published normal and hypertensive AP values in pregnancy, especially when decisions such as diagnosis of hypertensive disorders, classification of severity of hypertension and decisions concerning subsequent treatment strategies are to be taken. The available published data on normal and hypertensive gravidas are based on auscultatory methods, and until data on Dinamap measurements are published, measurements should be corrected using the above regression equations, or more simply by adding 10 mm Hg to the Dinamap diastolic measurement. Alternatively, the definition and classification of hypertension in pregnancy may be revised when Dinamap measurements are recorded, and 80 instead of 90 mm Hg may be regarded as a diastolic AP threshold for close monitoring, and 100 rather than 110 mm Hg as a diastolic AP threshold for urgent therapeutic intervention.

REFERENCES

1. Silas JH, Barker AT, Ramsay LE. Clinical evaluation of Dinamap 845 automated blood pressure recorder. *British Heart Journal* 1980; **43**: 202–205.
2. Weaver MG, Park MK, Lee D-H. Differences in blood pressure levels obtained by auscultatory and oscillometric methods. *American Journal of Diseases of Children* 1990; **144**: 911–914.
3. Ramsey M III. Noninvasive automatic determination of mean arterial pressure. *Medical and Biological Engineering and Computing* 1979; **17**: 11–18.
4. Yelderman M, Ream AK. Indirect measurement of mean blood pressure in the anesthetized patient. *Anesthesiology* 1979; **50**: 253–256.
5. Friesen RH, Lichtor JL. Indirect measurement of blood pressure in neonates and infants utilizing an automatic noninvasive oscillometric monitor. *Anesthesia and Analgesia* 1981; **60**: 742–745.
6. Kimble KJ, Darnall RA, Yelderman M, Ariagno RL, Ream AK. An automated oscillometric technique for estimating mean arterial pressure in critically ill newborns. *Anesthesiology* 1981; **54**: 423–426.
7. Hutton P, Dye J, Prys-Roberts C. An assessment of the Dinamap 845. *Anaesthesia* 1984; **39**: 261–267.
8. Runcie CJ, Reeve WG, Reidy J, Dougall JR. Blood pressure measurement during transport; a comparison of direct and oscillotonometric readings in critically ill patients. *Anaesthesia* 1990; **45**: 659–665.
9. Gravlee GP, Brockschmidt JK. Accuracy of four indirect methods of blood pressure measurement, with hemodynamic correlations. *Journal of Clinical Monitoring* 1990; **6**: 284–298.
10. Marx GF, Sofair DR, Winikoff SI. Blood pressure values in parturients: auscultatory versus oscillatory values. *Anesthesia and Analgesia* 1991; **72**: 562–563.
11. Friedman EA, Neff RK. *Pregnancy Hypertension; A Systematic Evaluation of Clinical Diagnostic Criteria.* Littleton, Massachussets: PSG Publishing 1977; 238.
12. Davey DA, MacGillivrary I. The classification and definition of the hypertensive disorders of pregnancy. *American Journal of Obstetrics and Gynecology* 1988; **158**: 892–898.
13. Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet* 1986; **1**: 307–310.
14. MacGillivrary I, Rose GA, Rowe B. Blood pressure survey in pregnancy. *Clinical Science* 1969; **37**: 395–407.

British Journal of Anaesthesia 1993; 70: 145–148

USE OF ULTRASOUND TO EVALUATE INTERNAL JUGULAR VEIN ANATOMY AND TO FACILITATE CENTRAL VENOUS CANNULATION IN PAEDIATRIC PATIENTS†

P. J. ALDERSON, F. A. BURROWS, L. I. STEMP AND H. M. HOLTBY

SUMMARY

Percutaneous cannulation of the internal jugular vein in paediatric patients may be technically difficult and is prone to complications. To investigate the possibility that anatomical factors contribute to these difficulties, we used a two-dimensional ultrasound scanner to examine venous anatomy in children aged up to 6 yr. We found that 18% of our children had anomalous venous anatomy that may account for some of the difficulties reported previously. The diameter of the internal jugular vein was predicted poorly by the patient's age ($r^2 = 0.259$) or weight ($r^2 = 0.155$). We also evaluated the use of this ultrasound scanner during percutaneous central venous cannulation in neonates and infants. Determining the course of the internal jugular vein with the scanner and then marking it on the overlying skin reduced both the time and number of needle insertions required to aspirate jugular venous blood and increased the chance of a complication-free cannulation. (Br. J. Anaesth. 1993; **70**: 145–148)

KEY WORDS

Anatomy: internal jugular vein. Anaesthesia: paediatric. Veins: cannulation, ultrasound.

The approach to central venous cannulation in children depends on the experience of the operator and the indication for catheterization. Situations that require definitive intrathoracic central venous placement merit techniques in which the success rate is high (cannulation of the internal jugular or subclavian vein) [1]. Many paediatric anaesthetists avoid a subclavian approach because of the report by Groff and Ahmed [2] describing five major complications of this approach when used in 44 children younger than 2 yr. Therefore, the internal jugular vein provides the best means of reliably achieving intrathoracic venous cannulation [3, 4], although cannulation by the internal jugular route is more difficult in children younger than 3 months of age or less than 4 kg in weight [4].

Denys and Uretsky [5] reported that anatomical variation in the position of the internal jugular vein in adults may complicate venous access by this route when a landmark-guided approach was used. A similar survey in children has not been conducted; indeed, little has been published on the anatomy of the internal jugular vein in paediatric patients [6].

Recent work has shown that two-dimensional ultrasound may assist the anaethetist in cannulating the internal jugular vein in adult patients [7–9]. This technique has been shown to increase the chance of successful cannulation, particularly at the first attempt. Significant reductions in the time taken to aspirate venous blood from the internal jugular vein and in the risk of accidental puncture of the carotid artery have been reported.

We have examined internal jugular venous anatomy and the use of ultrasound to facilitate jugular venous cannulation in neonates and infants.

PATIENTS AND METHODS

Approval was obtained from the Human Subjects Review Committee of the hospital.

Part 1

The object of the first part of the study was to determine if variations in the anatomy of the internal jugular vein could account for some of the difficulty experienced during landmark-guided percutaneous jugular venous catheterization in children.

We studied 50 patients younger than 6 yr undergoing cardiac surgery. The age (days) and weight (kg) of each patient were recorded. After induction of anaesthesia and nasotracheal intubation, the patient was positioned as if for cannulation of the right internal jugular vein: a rolled towel was placed under the shoulders, the head turned to the left and the table tilted head-down by 15°. Various characteristics of venous anatomy were examined with a portable, battery-operated, two-dimensional ultrasound scanner (Dymax Corporation, Pittsburgh, PA), which has a mechanical liquid-path 7.5-MHz transducer that allows high resolution imaging of structures up to 40 mm deep to the skin. We examined the relationship between the internal

---

P. J. ALDERSON, M.A., M.B., B.S.; F. A. BURROWS, M.D., F.R.C.P.C.; L. I. STEMP*, M.D.; H. M. HOLTBY, M.B., B.S., F.R.C.P.C.; Department of Anaesthesia, Room 2303, The Hospital for Sick Children and the Research Institute of the University of Toronto, 555 University Avenue, Toronto, Ontario, Canada M5G 1X8. Accepted for Publication: September 4, 1992.

*Present address: The Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, Ohio, U.S.A.

Correspondence to F.A.B.

†Presented in part at the annual meeting of the American Society of Anesthesiologists, New Orleans, Louisiana, U.S.A., October 1992.

jugular vein and the carotid artery from the angle of the mandible to the clavicle, and the diameter and depth of the internal jugular vein at the level of the cricoid cartilage. Diameter and depth were measured to the nearest 0.5 mm with a pair of calipers applied to the image on the scanner screen.

Part 2

The object of the second part of the study was to determine if the use of such an ultrasound scanner could facilitate percutaneous internal jugular vein cannulation in neonates and infants.

We studied 40 patients younger than 2 yr who would undergo percutaneous insertion of an internal jugular cannula during cardiac surgery. None had undergone prior cardiac surgery or jugular cannulation. They were allocated randomly to one of two groups: group A = cannulation guided by anatomical landmarks; group B = cannulation guided by ultrasound.

All central venous cannulations were carried out after induction of anaesthesia and nasotracheal intubation. The patient was positioned for cannulation of the right internal jugular vein with a rolled towel under the shoulders, the head turned to the left and the table titled head-down by 15°. For those in group A, the two heads of the sternomastoid were palpated, the position of the carotid artery verified and the cannula inserted at the junction of the two heads of the sternomastoid angled toward the ipsilateral nipple. For those in group B, the ultrasound scanner was used to visualize the internal jugular vein so that its projection could be marked onto the overlying skin with a pen; this line then served as a guide for cannulation.

In every patient, cannulation was carried out by an experienced cardiac anaesthetist who used a 21-gauge, 4-cm needle to locate the internal jugular vein. A 16-gauge polyurethane double-lumen catheter was positioned using a Seldinger wire passed through the 21-gauge needle. The time from the initial skin puncture to the aspiration of venous blood was recorded, together with the number of needle insertions required to locate the vein. Details of any complications were noted.

Data analysis

Data are presented as arithmetic means (SD). The lines of best fit for the graphical figures were determined by linear regression analysis. Parametric data were analysed by one-way analysis of variance and the Student–Newman–Keuls test. $P < 0.05$ was considered to be significant.

RESULTS

Part 1

The patients ranged in age from 3 days to 5.5 yr and in weight from 2.7 to 22 kg. None of the children had been born prematurely.

In 82 % of patients, the internal jugular vein ran antero-laterally to the carotid artery. In 4 %, the vein was in a similar position relative to the carotid artery, but was of unusually small diameter (defined as ≤ 3 mm for neonates and infants and as ≤ 5 mm for older children). In 10 %, the vein ran so medially that it entirely overlay the carotid artery; in 2 % the vein ran widely lateral to the carotid artery. In the remaining 2 %, the vein could not be seen.

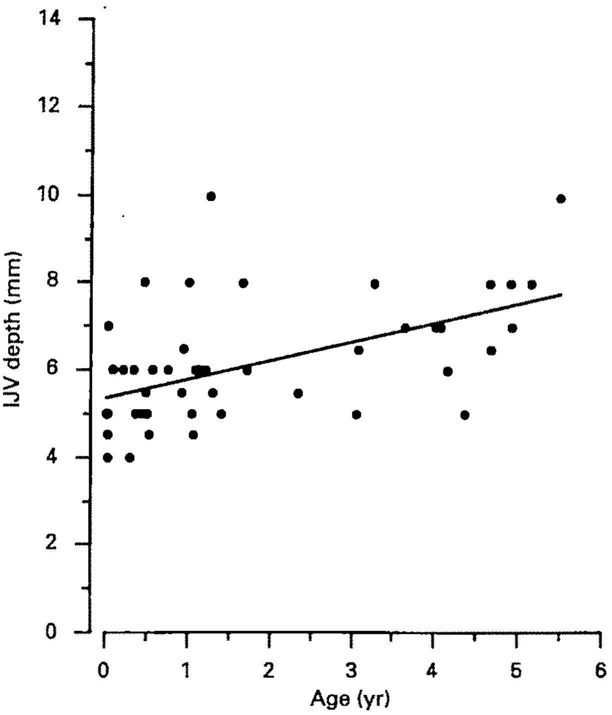


FIG. 1. Relationship of the depth of the internal jugular vein (IJV) to age. $r^2 = 0.290$.

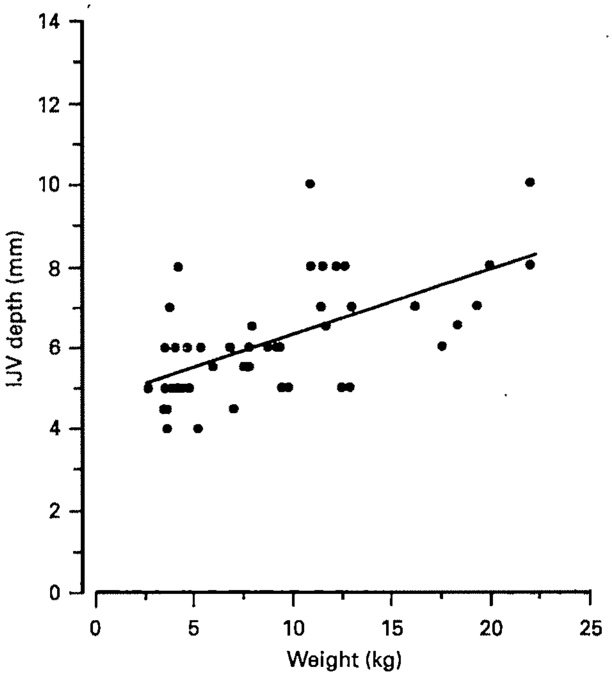


FIG. 2. Relationship of the depth of the internal jugular vein (IJV) to weight. $r^2 = 0.379$.

At the level of the cricoid ring, the vein was seen 4–10 mm below the surface of the skin. This distance tended to increase with both age and weight, the better correlation being with weight (figs 1, 2). At the same site, the vein varied in diameter from 2.5 to 12 mm; again, vein size tended to increase with both age and weight, but correlations were poor (figs 3, 4).

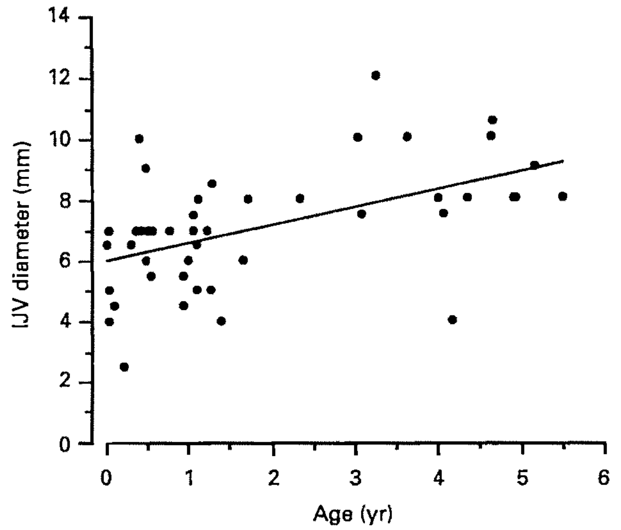


FIG. 3. Relationship of the diameter of the internal jugular vein (IJV) to age. $r^2 = 0.259$.

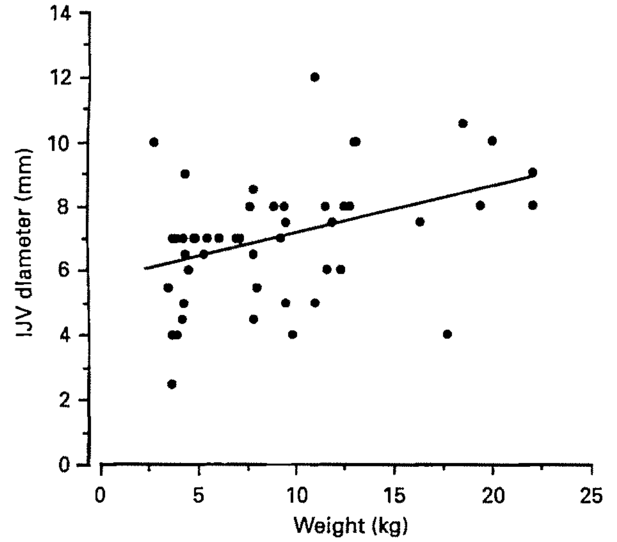


FIG. 4. Relationship of the diameter of the internal jugular vein (IJV) to weight. $r^2 = 0.155$.

TABLE I. *Comparison of landmark-guided and ultrasound-guided cannulation techniques (range or mean (SD)).* $P < 0.05$ compared with group B*

Access data	Group A Landmark-guided	Group B Ultrasound-guided
Success rate	16/20	20/20
Time taken (s)	6–170	2–90
Time taken (s)	56.4 (48.9)*	23.0 (27.4)
No. needle insertions	2.0 (1.0)*	1.35 (0.7)

Part 2

The two groups were similar in age and weight (group A: 281 (218) days, 6.8 (2.5) kg; group B: 258 (170) days, 6.6 (2.5) kg). Each group contained three neonates and 17 infants.

Table I compares the success of the two cannulation techniques. In four of the children assigned to group A, the internal jugular vein was not located. In the other 16 patients, it took significantly longer ($P = 0.011$) to locate the vein than in those in group B in whom ultrasound was used to mark the course of the vein. In addition, significantly more needle insertions ($P = 0.018$) were needed to locate the vein in group A patients.

The most common complication during cannulation was inability to pass the Seldinger wire into the superior vena cava after venous blood had been aspirated. This occurred eight times in group A and three times in group B. Carotid artery puncture occurred in two patients in group A and in one in group B. Overall, eight cannulations in group A and 16 in group B were uncomplicated ($P < 0.05$).

DISCUSSION

Eighteen percent (nine of 50) of the patients younger than 6 yr in our study had anatomical factors that may complicate a landmark-guided approach to the internal jugular vein.

In a previous prospective study [10] of landmark-guided percutaneous internal jugular venous catheterization in children aged up to 14 yr, the right internal jugular vein was cannulated successfully in 31 of 52 patients (59.6%), and the left in nine of 52. Greater success rates were obtained with children older than 2 yr, although this finding was not statistically significant. The complications noted included 12 (23%) carotid artery punctures. In a retrospective study [11] of percutaneous jugular venous catheterization in 200 children, 45% of whom were 5 yr or younger, the internal jugular vein was cannulated successfully in 109 of 128 patients (85.2%). The recent Osaka study [4] of 106 children aged up to 7 yr reported that the rate of successful cannulation on the first attempt, defined so that it included multiple needle insertions at a single site, was 78.3%. Complications included 12 (11.3%) arterial punctures.

From these studies it appears that the proportion of patients in whom percutaneous internal jugular cannulation is difficult is of the same magnitude as the proportion of patients in whom the relationship between the vein and the carotid artery is anomalous in some way.

Venous blood is often identified during cannulation as the needle is drawn back through the vein. As we have found that the carotid artery runs posterior to the vein in 10% of the children in our study, we suggest that the risk of carotid puncture is of this magnitude. This risk appears to be similar to the rates of arterial puncture in the research cited above.

There is little information on the diameter of the internal jugular vein in childhood. One anatomical survey [6] included 11 children aged from 13 months to 16 yr. This subset showed a poor correlation between the diameter of the internal jugular vein and age, height, weight or body surface area. The smallest vein seen in these children was 6.6 mm in diameter when the child was in the Trendelenburg position. Their anatomical findings are similar to those reported here.

Inability to demonstrate an internal jugular vein in 2% of our patients was surprising: congenital absence of the internal jugular vein is extremely rare, particularly in the absence of other cerebrovascular malformations. There are two possible explanations for our result: the ultrasound scanner could not identify the internal jugular vein because the diameter was so small, or the ultrasound probe occluded the vein because, despite our efforts, the probe exerted excessive pressure on the neck.

In comparison with group A in our study, both the time required to locate the internal jugular vein and the number of needle insertions required were less in group B. These findings concur with those of earlier reports in adult patients [7–9], indicating that ultrasound guidance improved the speed and safety of central venous access. In previous studies the ultrasound probe was wrapped in a sterile sheath so that it could be manipulated in the sterile field by the operator during cannulation. Although this technique allows the operator to guide the needle into the vein visually, it requires the extra expense of the sterile sheath and a considerable degree of manual dexterity in paediatric practice. We found that our simplified approach, without the sheath, was also effective.

Using the ultrasound scanner, we found that our complication rate was 20%, compared with 60% when using the landmark approach. Our most common complication was inability to insert the Seldinger wire into the superior vena cava. Other studies have not reported this as a complication, although it can greatly increase the overall time required to place the central catheter. The reason for the high incidence of difficulty inserting the Seldinger wire in neonates and infants is probably the ease with which the needle tip becomes displaced from the lumen of the vein as the syringe is disconnected from the needle. We were unable to show that the rate of carotid puncture was reduced with the use of ultrasound because of our small sample size.

ACKNOWLEDGEMENTS

We thank Dymax Corporation for loan of the Site Rite ultrasound scanner for the duration of these studies.

REFERENCES

1. Motoyama EK, ed. *Smith's Anesthesia for Infants and Children*, 5th Edn. St Louis: CV Mosby Co., 1990; 242–243.
2. Groff DB, Ahmed N. Subclavian vein catheterization in the infant. *Journal of Pediatric Surgery* 1974; **9**: 171–174.
3. Postel JP, Quintard JM, Ricard J, Delaplace R, Bernard F, Canarelli JP. Elaboration d'une technique sûre d'accès veineux central en pédiatrie. Notre expérience de 700 cathéters centraux percutanés. *Chirurgie Pédiatrique* 1990; **31**: 219–222.
4. Hayashi Y, Uchida O, Takaki O, Ohnishi Y, Nakajima T, Kataoka H, Kuro M. Internal jugular vein catheterization in infants undergoing cardiovascular surgery: An analysis of the factors influencing successful catheterization. *Anesthesia and Analgesia* 1992; **74**: 688–693.
5. Denys BG, Uretsky BF. Anatomical variation of internal jugular vein position: Impact on venous access. *Circulation* 1990; **82** (Suppl.): III-68.
6. Mortensen JD, Talbot S, Burkart JA. Cross-sectional internal diameters of human cervical and femoral blood vessels: Relationship to subject's sex, age, body size. *Anatomical Record* 1990; **225**: 115–124.
7. Denys BG, Uretsky BF, Reddy PS, Ruffner RJ, Sandhu JS, Breishlatt WM. An ultrasound method for safe and rapid central venous access. *New England Journal of Medicine* 1991; **324**: 566.
8. Troianos CA, Jobes DR, Ellison N. Ultrasound-guided cannulation of the internal jugular vein. A prospective, randomized study. *Anesthesia and Analgesia* 1991; **72**: 823–826.
9. Koski EMJ, Suhonen M, Mattila MAK. Ultrasound-facilitated central venous cannulation. *Critical Care Medicine* 1992; **20**: 424–426.
10. Prince SR, Sullivan RL, Hackel A. Percutaneous catheterization of the internal jugular vein in infants and children. *Anesthesiology* 1976; **44**: 170–174.
11. Nicolson SC, Sweeney MF, Moore RA, Jobes DR. Comparison of internal and external jugular cannulation of the central circulation in the pediatric patient. *Critical Care Medicine* 1985; **13**: 747–749.

British Journal of Anaesthesia 1993; **70**: 149–153

METABOLIC EFFECTS OF CORRECTIVE SURGERY IN INFANTS AND CHILDREN WITH CONGENITAL HEART DEFECTS

K. PUHAKKA, J. RÄSÄNEN, M. LEIJALA AND K. PELTOLA

SUMMARY

We have measured oxygen consumption and carbon dioxide production by indirect calorimetry in 25 infants and children immediately before and after surgical correction of congenital cardiac malformations. Surgical correction of the cardiac defect caused a decrease in oxygen consumption towards normal. Greatly increased oxygen consumption values were observed before surgery in the infants with a large left-to-right intracardiac shunt and heart failure and the highest reduction in metabolic rate, up to 43%, was observed in these infants. The results indicate that corrective surgery for congenital cardiac malformations reduces the load on the cardiopulmonary system immediately after operation. (Br. J. Anaesth. 1993; **70**: 149–153)

KEY WORDS

Heart: congenital defects. Oxygen: consumption. Surgery: cardiac, paediatric.

In congenital heart disease, oxygen consumption is increased in patients with intracardiac or extracardiac left-to-right shunt and excessive pulmonary flow, while those with right-to-left shunt or no shunt have normal or reduced pulmonary flow and normal or reduced oxygen consumption [1–6]. Infants with a large intracardiac left-to-right shunt require early surgical intervention because of failure to thrive and congestive heart failure.

Previous reports indicate that the secondary metabolic effects of congenital cardiac defects are frequently reversible if the lesion is surgically corrected [7–10]. Surgical correction of the cardiac malformation alters the relationship between the pulmonary and systemic flows towards that prevailing in the normal circulating system, and should also adjust the metabolic rate. The metabolic changes that take place during postoperative recovery have not been well documented, however.

This investigation was designed to assess the effect of corrective operations on oxygen consumption and carbon dioxide production immediately after surgery in infants and children with cyanotic and acyanotic cardiac lesions.

PATIENTS AND METHODS

We studied 25 consecutively admitted infants and children undergoing elective open heart operations for the correction of congenital heart defects. Patients who needed supplementary oxygen therapy or mechanical ventilation before surgery were excluded. The investigation was approved by the Institutional Ethics Committee of Helsinki University Children's Hospital, and informed consent was obtained from one or both parents of each patient.

The patients fasted for 4–5 h and were premedicated with oral flunitrazepam 100 μg kg^{-1} (maximum dose 2 mg) before operation. While the children were asleep, oxygen consumption and carbon dioxide production during spontaneous breathing were measured using an open system indirect calorimetry device [11] (Datex Deltatrac Paediatric, Datex Inc., Helsinki, Finland) in which the ventilatory gases were collected using a canopy from which a constant flow of gas (10 litre min^{-1}) was drawn into the monitor. The gas lost from the canopy was replaced by an inflow of room air through a vent at the top, and inspiratory gas fractions were sampled outside the canopy at the vent inlet. The differences between the inspired and expired oxygen fractions were measured using a fast-response, paramagnetic differential oxygen sensor (OM-101, Datex/Instrumentarium, Helsinki, Finland) and the inspired and expired carbon dioxide fractions were measured using an infra-red carbon dioxide sensor. The calorimeter was calibrated before each measurement according to the instructions supplied by the manufacturer.

The canopy covered the child's head, shoulders and upper chest, and the escape of the expiratory gases from under it was prevented by a soft plastic skirt which was attached to the rim of the canopy. After a 10-min stabilization period, oxygen consumption and carbon dioxide production were measured once every 1 min for 15 min. If the patient's movements interfered with the measurement, additional sedation with i.m. ketamine 3 mg kg^{-1} or rectal methohexitone 10 mg kg^{-1} was given and data collection was restarted. Arterial blood oxyhaemoglobin saturation was monitored continuously using a pulse oximeter. Heart rate,

---

K. PUHAKKA, M.D., Department of Anaesthesiology, Oulu University Central Hospital, Kajaanintie 50, SF-90220 Oulu 22, Finland. J. RÄSÄNEN, M.D., Department of Anesthesiology, University of South Florida College of Medicine, Tampa, Florida, U.S.A. M. LEIJALA, M.D. (Department of Surgery); K. PELTOLA, M.D. (Department of Anaesthesiology); University Children's Hospital, Helsinki, Finland. Accepted for Publication: August 24, 1992.

Correspondence to K.P.

ventilatory frequency, rectal temperature and room temperature were recorded during the collection of ventilatory gases. Blood haemoglobin concentration, measured the day before the operation, was obtained from the medical records.

After the operation, the measurements were repeated after tracheal extubation as soon as the patient maintained an arterial blood oxyhaemoglobin saturation greater than 90% when breathing room air. The measurements were performed during the late morning hours, when the child was asleep or sedated with i.v. morphine 100 μg kg^{-1} or flunitrazepam 30 μg kg^{-1}.

A two-way repeated measures analysis of variance was used to test the statistical significance of the effects of age and type of malformation on the variables. Student's *t* test for paired observations was used to assess the statistical significance of changes within the groups; probability values < 0.05 were considered statistically significant.

The measured values for oxygen consumption ($\dot{V}O_2$) and carbon dioxide production ($\dot{V}CO_2$) were compared with the expected values calculated from the regression equation published by Lindhal [12] ($\dot{V}O_2$ ml min^{-1} = 5.0 × weight (kg) + 19.8; $\dot{V}CO_2$ ml min^{-1} = 4.8 × weight (kg) + 6.4).

Multiple linear regression analysis was used to evaluate the influence of age, type of cardiac malformation, duration of cardiopulmonary bypass, time of postoperative data collection, preoperative heart failure, rectal temperature and change in ventilatory frequency and heart rate on the change in oxygen consumption. The results are expressed as mean (SD).

RESULTS

The patients ranged in age from 2 months to 10 yr. Fifteen of the 25 patients had a left-to-right intracardiac shunt, one had isolated aortic stenosis and nine had a cyanotic cardiac malformation (tables I, II).

Two patients (Nos 5 and 9) received rectal methohexitone and four (Nos 3, 6, 13 and 24) received i.m. ketamine as additional sedation for the measurements before surgery. Fifteen patients had been treated for cardiac failure before surgery and 20 needed inotropic support at the time of postoperative data collection.

The measurements after surgery were performed between the first and the 15 days after operation. Two patients were receiving total parenteral nutrition at this time, and the other 23 were receiving enteral feeding supplemented with 5–10% glucose infusions. Mean room temperature was 24.9 (1.6) °C during all the examinations.

The patients were classified into two subgroups according to the presence or absence of a cyanotic cardiac lesion before surgery. Changes in the variables in the two groups are shown in table III.

The mean oxygen consumption of the infants aged 1 yr or less was 11.0 (3.3) ml kg^{-1} min^{-1} before operation and 7.8 (1.3) ml kg^{-1} min^{-1} afterwards ($P < 0.01$) and that of the children older than 1 yr

TABLE I. *Clinical characteristics of the patients.* $\dot{Q}p:\dot{Q}s$ = *Relationship between pulmonary and systemic flows; *cardiac failure before operation; TOF = tetralogy of Fallot; TGA = transposition of the great arteries; AVSD = atrioventricular septal defect; VSD = ventricular septal defect; PH = pulmonary hypertension; ASD = atrial septal defect; PDA = patent ductus arteriosus; UVH = univentricular heart; PA = pulmonary atresia; AS = aortic stenosis; RV–PA = right ventricle–pulmonary artery; FAS = fetal alcoholic syndrome; SDown = Down syndrome*

Patient No.	Diagnosis	$\dot{Q}:\dot{Q}$	Procedure
1	TOF	1:1	Total correction
2	TGA	1:1	Senning's procedure
3	AVSD, SDown	4.5:1*	Total correction
4	AVSD, SDown	1.2:1*	Total correction
5	VSD	3.1:1	Closure
6	VSD (multiple) ASD, PDA, SDown	> 10:1*	Closure, ligation
7	ASD, VSD, SDown	> 10:1*	Closure
8	AVSD, SDown	10:1*	Total correction
9	AVSD, SDown	3.1:1*	Total correction
10	AVSD	10:1*	Total correction
11	VSD, PDA, PH	10:1*	Closure, ligation
12	AS	1:1	Valvotomy
13	VSD	4.1:1*	Closure
14	PA, VSD	1:1	Total correction
15	UVH, TGA	1:1*	Septation
16	PA, VSD, PDA	1:1*	RV–PA homograft Ligation
17	UVH, TGA	1:1*	Fontan's procedure
18	UVH	1:1*	Fontan's procedure
19	TOF, FAS	3.4:1	Total correction
20	TOF	1:1	Total correction
21	ASD	1.6:1	Closure
22	ASD	4.5:1	Closure
23	VSD	1.9:1	Closure
24	VSD	5.8:1*	Closure
25	VSD	> 3:1	Closure
Mean (SD)		3.8 (3.4)	

TABLE II. *Patients' age and weight and oxygen consumption* ($\dot{V}O_2$) *before and after cardiac operation*

Patient No.	Age (yr)	Weight (kg)	$\dot{V}O_2$ (ml kg^{-1} min^{-1}) Before op.	$\dot{V}O_2$ (ml kg^{-1} min^{-1}) After op.
1	0.67	7.8	8.21	6.28
2	0.42	8.1	6.79	6.67
3	1.00	6.9	9.28	8.12
4	1.00	8.1	9.38	8.40
5	1.00	6.9	9.86	6.96
6	0.80	6.9	10.15	8.99
7	0.58	5.5	11.46	7.09
8	0.50	4.2	13.33	7.86
9	0.50	5.0	10.00	7.40
10	0.36	3.9	14.87	8.46
11	0.33	4.2	16.19	9.52
12	0.30	6.1	6.89	5.74
13	0.12	3.4	16.77	10.0
14	9.00	25.8	4.26	4.34
15	9.00	19.0	6.42	7.21
16	5.00	17.0	7.41	6.77
17	4.00	15.3	6.54	5.43
18	4.00	15.1	7.95	4.77
19	2.50	10.4	9.52	7.50
20	2.00	14.3	7.90	5.73
21	8.00	27.0	4.22	5.15
22	7.00	15.8	4.81	6.08
23	6.00	15.8	5.57	7.41
24	2.00	8.8	9.78	7.73
25	10.00	24.2	3.88	3.88
Mean (SD)	3.0 (3.3)	11.4 (7.1)	8.86 (3.56)	6.94 (1.57)

TABLE III. *Mean* (SD) *oxygen consumption* ($\dot{V}O_2$), *carbon dioxide production* ($\dot{V}CO_2$), *heart rate* (*HR*), *ventilatory frequency* (f), *blood haemoglobin concentration* (*Hb*), *rectal temperature* (*Temp.*) *and peripheral oxygen saturation* (Sp_{O_2}) *in patients with cyanotic and acyanotic cardiac disease before and after corrective surgery*

	Cyanotic heart disease ($n = 9$)			Acyanotic heart disease ($n = 16$)		
	Before surgery	After surgery	*P*	Before surgery	After surgery	*P*
$\dot{V}O_2$ (ml kg^{-1} min^{-1})	7.2 (1.5)	6.1 (1.1)	< 0.05	9.8 (4.1)	7.4 (1.6)	< 0.01
$\dot{V}CO_2$ (ml kg^{-1} min^{-1})	5.8 (1.2)	4.7 (1.0)	< 0.05	7.4 (2.9)	5.6 (1.3)	< 0.01
HR (beat min^{-1})	99 (24)	113 (17)	ns	126 (22)	125 (12)	ns
f (b.p.m.)	38 (19)	34 (10)	ns	55 (21)	39 (13)	< 0.01
Hb (g $litre^{-1}$)	153 (25)	121 (15)	< 0.01	126 (20)	123 (13)	ns
Temp. (°C)	36.7 (0.3)	37.0 (0.7)	ns	36.8 (0.6)	37.6 (0.6)	< 0.01
Sp_{O_2}	82 (10)	89 (6)	ns	92 (4)	93 (2)	ns

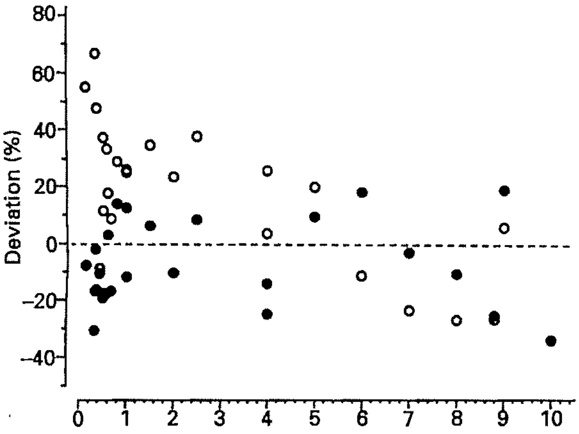


FIG. 1. Plots of the difference between observed and expected oxygen consumption (Deviation) before (○) and after (●) corrective surgery, against age in 25 children with congenital cardiac malformations.

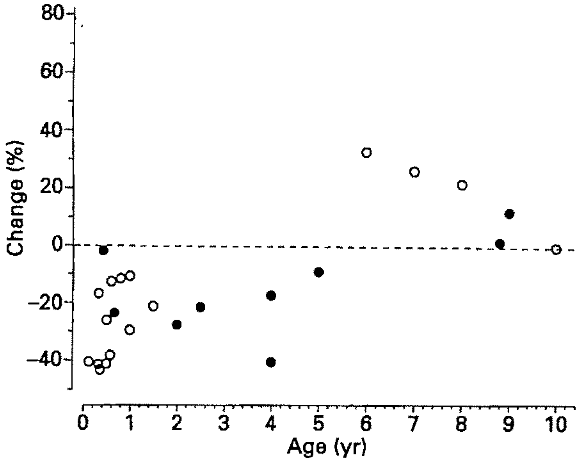


FIG. 2. Effect of surgical correction of cardiac malformation on oxygen consumption (Change) in children with cyanotic (●) ($n = 9$) and acyanotic (○) ($n = 16$) heart disease.

was 6.5 (2.0) ml kg^{-1} min^{-1} before and 6.0 (1.3) ml kg^{-1} min^{-1} after operation. The preoperative oxygen consumption of the infants was significantly greater than that expected for their weight (8.6 (1.1) ml kg^{-1} min^{-1}) ($P < 0.01$), but there was no longer any significant difference after the corrective operation. Both preoperative and postoperative oxygen consumption were similar to the expected values (6.3 (0.4) ml kg^{-1} min^{-1}) (ns) in the case of the children aged more than 1 yr. The deviations of oxygen consumption values from the expected values are presented in figure 1.

The changes in carbon dioxide production in response to the operation were similar to those in oxygen consumption.

The mean decline in oxygen consumption for all patients after surgery was 15 (22) %, range −43 % to +33 % ($P < 0.01$) (fig. 2), and that in carbon dioxide production 17 (22) %, range −46 % to +35 % ($P < 0.001$).

The type of cardiac malformation (cyanotic/acyanotic) did not correlate with the change in oxygen consumption (fig. 2), the only significant predictor of the latter being age ($r = 0.72$). The decrease in oxygen consumption after surgery was greater in the 15 patients with cardiac failure before surgery (23 (18) %) than in the 10 without cardiac failure (4 (24) %) ($P < 0.05$).

DISCUSSION

Oxygen consumption and carbon dioxide production were measured in 25 infants and children with congenital heart defects immediately before and after surgical correction of cardiac malformation in order to evaluate changes in metabolic rate. Although an increased incidence of preoperative hypermetabolism was found in the infants and small children, a quick reversion to normal values occurred after the operation. Comparison of the measured oxygen consumption and carbon dioxide production values with those expected in healthy, anaesthetized, spontaneously breathing children of comparable weight [12] revealed an abnormal increase in the metabolic rate, of a type which could only have resulted from measurement error or some factor related to the cardiopulmonary disease.

All measurements were performed by one of two investigators (K.P., J.R.) using the same open system indirect calorimetry device, which was calibrated carefully before each measurement. A validation of this device has been published previously [11]. It is therefore unlikely that any difference in the equipment or its use could have led to a systematic error.

There are several factors which may alter the metabolic rate. All our patients were sedated and sleeping during both measurements in order to standardize the conditions, as activity can quickly increase body oxygen consumption [13–16] and sedation reduces it by 26–34% [15, 17]. The type of sedation has also been shown to influence oxygen consumption during cardiac catheterization [18]. Additional sedation was selected according to the patient's clinical condition, to restore spontaneous breathing and stable haemodynamic state and to eliminate active muscle movements. Theoretically, ketamine increases the metabolic rate [18], but we used a small dose without atropine. The overall result—a decrease in metabolic rate—does not alter, however, even if these patients are excluded. Methohexitone, in contrast, may reduce metabolism. In spite of this, patients Nos 5 and 9 had an abnormally increased oxygen consumption before surgery and there was a decrease after surgery.

Body temperature [19] and environmental temperature [20, 21] are also known to modify metabolism. Rectal temperature was the same or greater after the operation in all the patients and therefore cannot explain the decrease in metabolic rate (table III). Room temperature was comparable for both measurement periods and the patients were dressed and covered in a similar way. Bed rest and inadequate caloric intake reduce the metabolic rate in healthy adults [22, 23] and a meal can increase it for several hours [13]. However, the present patients had been fasting for 4–5 h before the preoperative examination. Admittedly, the food intake was not standardized for the postoperative measurement, and some measurements were performed soon after a meal, but any errors resulting from differences in feeding would have increased the postoperative oxygen consumption in relation to the preoperative values, and thus cannot explain the observed reduction in oxygen consumption.

Similarly, surgical trauma initiates many neuroendocrine responses which tend to increase the metabolic rate during postoperative recovery from major surgery [19, 24], and infants and children have been shown to have greater hormonal responses of shorter duration than adults after cardiac surgery [25–27]. The day of postoperative measurement in this series varied between the first and the 15th, depending on patient's clinical condition. Nine patients were examined during the first 3 days after the operation, when the effect of surgical trauma on the metabolic rate is greatest. In three of these (patients Nos 21, 22, 23, aged between 6 and 8 yr), the metabolic rate was normal before surgery and increased afterwards, secondary to surgical stress. Differences in neuroendocrine function thus do not explain the decrease in oxygen consumption resulting from the operation.

It has been shown that patients with congenital heart defects involving high pulmonary flow, large left-to-right shunt and cardiac failure have increased oxygen consumption because of increased cardiopulmonary work [3–5, 28, 29] and this was seen also in our study, in which the decrease in metabolic rate occurred exclusively in the infants and small children with congestive heart failure requiring treatment before the operation. Although infants with cyanotic cardiac malformations have been shown to have smaller oxygen consumption in relation to body weight than normal infants, because of limited oxygen transport capacity and reduced pulmonary blood flow [1, 2, 4–6], our patients with cyanotic cardiac malformations had increased or normal oxygen consumption before surgery.

Decreased oxygen supply cannot explain the decrease in oxygen consumption after the operation in this study, because the patients were in good clinical condition at the time of the postoperative examination, spontaneously breathing room air, and in a resting state. Our findings suggest that the metabolic effects of corrective operations are more pronounced in small children than in older ones, but this seems to be a consequence of selecting patients with symptoms of cardiopulmonary failure for operation at an early age. These patients appear to have an increased metabolic rate in response to excessive cardiopulmonary work [29]. Corrective surgery relieved the increased cardiopulmonary load within a few days, thereby causing a reduction in total body oxygen consumption. This improvement in metabolic rate may explain the greater weight gain of infants and children after corrective surgery, as observed in earlier long-term follow-up studies [7, 9].

ACKNOWLEDGEMENTS

This work was supported by grants from the Academy of Finland and the Alma and K. A. Snellman Foundation, Oulu, Finland.

REFERENCES

1. Cayler GG, Rudolf AM, Nadas AS. Systemic blood flow in infants and children with and without heart disease. *Pediatrics* 1963; **32**: 186–201.
2. Levison H, Delivoria-Papadopoulos M, Swyer PR. Variations in oxygen consumption in the infant with hypoxaemia due to cardiopulmonary disease. *Acta Paediatrica Scandinavica* 1965; **54**: 369–374.
3. Lees MH, Bristow JD, Griswold HE, Olmsted RW. Relative hypermetabolism in infants with congenital heart disease and undernutrition. *Pediatrics* 1965; **36**: 183–191.
4. Kennaird DL. Oxygen consumption and evaporative water loss in infants with congenital heart disease. *Archives of Diseases in Childhood* 1976; **51**: 34–41.
5. Lister G, Talner NS. Oxygen transport in congenital heart disease. *Cardiovascular Clinics* 1981; **11**: 129–148.
6. Berman W, Wood SC, Yabek SM, Dillon T, Fripp RR, Burstein R. Systemic oxygen transport in patients with congenital heart disease. *Circulation* 1987; **75**: 360–368.
7. Cartmill TB, DuShane JW, McGoon DC, Kirklin JW. Results of repair of ventricular septal defect. *Journal of Thoracic and Cardiovascular Surgery* 1966; **52**: 486–501.
8. Goldberg SJ, Adams FH, Hurwitz RA. Effect of cardiac surgery on exercise performance. *Journal of Pediatrics* 1967; **71**: 192–197.
9. Barrat-Boyes BG, Neutze JM, Clarkson PM, Shardey GC, Brandt PWT. Repair of ventricular septal defect in the first two years of life using profound hypothermia–circulatory arrest techniques. *Annals of Surgery* 1976; **184**: 376–390.
10. Whitmer JT, James FW, Kaplan S, Schwartz DC, Sandker Knight MJ. Exercise testing in children before and after surgical treatment of aortic stenosis. *Circulation* 1982; **63**: 254–263.
11. Takala J, Keinänen O, Väisänen P, Kari A. Measurement of gas exchange in intensive care: Laboratory and clinical validation of a new device. *Critical Care Medicine* 1989; **17**: 1041–1047.
12. Lindahl GE. Oxygen consumption and carbon dioxide elimination in infants and children during anaesthesia and surgery. *British Journal of Anaesthesia* 1989; **62**: 70–76.
13. Strand FL. Energy balance: regulation of body temperature, food and water intake and metabolism. In: Strand FL, ed. *Physiology*. N.Y: Collier Macmillan Publ., 1983; 441–462.

14. Holliday MA, Potter D, Jarrah A, Bearg S. The relation of metabolic rate to body weight and organ size. *Pediatric Research* 1967; **1**: 185–195.
15. Weissman C, Kemper M, Damask MC, Askanazi J, Hyman AI, Kinney JM. Effect of routine intensive care interactions on metabolic rate. *Chest* 1984; **86**: 815–818.
16. Wessel HU, Rorem D, Muster AJ, Acevedo RE, Paul MH. Continuous determination of oxygen uptake in sedated infants and children during cardiac catheterization. *American Journal of Cardiology* 1969; **24**: 376–385.
17. Baum D, Brown AC, Church SC. Effect of sedation on oxygen consumption of children undergoing cardiac catheterization. *Pediatrics* 1967; **39**: 891–895.
18. Fixler DE, Carrell T, Browne R. Oxygen consumption in infants and children during cardiac catherization under different sedation regimens. *Circulation* 1974; **50**: 788–794.
19. Roe CF. Temperature regulation and energy metabolism in surgical patients. *Progress in Surgery* 1973; **12**: 96–127.
20. Hey E. Thermal neutrality. *British Medical Bulletin* 1975; **31**: 69–74.
21. Hardy JD. Physiology of temperature regulation. *Physiological Reviews* 1961; **41**: 521–606.
22. Askanazi J, Carpentier YA, Jeevandam M, Michelsen CB, Elwyn DH, Kinney JM. Energy expenditure, nitrogen balance, and norepinephrine excretion after injury. *Surgery* 1981; **89**: 478–484.
23. Gump FE, Martin P, Kinney JM. Oxygen consumption and caloric expenditure in surgical patients. *Surgery, Gynecology and Obstetrics* 1973; **137**: 499–513.
24. Shizgal HM. Metabolic response to surgery: essentials. *Baillière's Clinical Anaesthesiology* 1989; **3**: 299–316.
25. Bevan JC. Metabolic response to surgery in children. *Baillière's Clinical Anaesthesiology* 1989; **3**: 349–364.
26. Milne EMG, Elliot MJ, Holden MP. The effect of intermediary metabolism of open-heart surgery with deep hypothermia and circulatory arrest in infants of less than 10 kilograms body weight. A preliminary study. *Perfusion* 1986; **1**: 29–40.
27. Anand KJS, Hansen DD, Hickey PR. Hormonal–metabolic stress responses in neonates undergoing cardiac surgery. *Anesthesiology* 1990; **73**: 661–670.
28. Lees MH, Way RC, Ross BB. Ventilation and respiratory gas transfer of infants with increased pulmonary blood flow. *Pediatrics* 1967; **40**: 259–271.
29. Pittman JG, Cohen P. The pathogenesis of cardiac cachexia. *New England Journal of Medicine* 1964; **271**: 403–409, 453–460.

British Journal of Anaesthesia 1993; **70**: 154–159

EFFECT OF NITROUS OXIDE ON CEREBRAL BLOOD FLOW IN NORMAL HUMANS

L. M. FIELD, D. E. DORRANCE, E. K. KRZEMINSKA AND L. Z. BARSOUM

SUMMARY

We have studied the effect of nitrous oxide on cerebral haemodynamics in 24 healthy male volunteers. Hemispherical cerebral blood flow (CBF) was measured using the xenon-133 inhalation technique, blood flow velocities in the right middle cerebral artery were calculated using transcranial Doppler ultrasound and the pulsatility index (PI)—the inverse of which is theoretically proportional to flow in the vessel under investigation—was derived from analysis of the spectrally analysed velocity pulse wave form obtained from the middle cerebral artery. Each variable was measured with the subject inhaling 100% oxygen (1st baseline), 30% nitrous oxide in oxygen, 100% oxygen (2nd baseline) and 60% nitrous oxide in oxygen. CBF was significantly greater with 30% ($0.01 > P > 0.001$) and 60% nitrous oxide ($P < 0.001$) compared with baseline, although the difference between 30% and 60% nitrous oxide was not significant. Changes in 1/PI correlated closely with those in hemispherical CBF. Blood flow velocities increased significantly with 30% ($P < 0.001$) and 60% nitrous oxide ($0.005 > P > 0.001$), the difference between 30% and 60% nitrous oxide also being significant ($0.005 > P > 0.001$). We observed a plateau in the change in CBF caused by nitrous oxide and suggest that this may be explained by activation of intact autoregulative mechanisms in healthy human brain. (Br. J. Anaesth. 1993; **70**: 154–159)

KEY WORDS

Anaesthetics, gases: nitrous oxide. Brain: cerebral blood flow. Measurement techniques: transcranial Doppler ultrasound.

After conflicting reports on the influence of nitrous oxide on cerebral haemodynamics in the 1960s and 70s [1–3], there has been much debate as to the advantages and disadvantages of this agent in neurosurgical anaesthesia [4]. In particular, there is accumulating evidence to show that nitrous oxide increases cerebral blood volume [5], intracranial pressure (ICP) [6–8] and cerebral blood flow (CBF) [7–13]. This is undesirable in neurosurgical practice and may adversely affect outcome. The evidence to date has been gathered from animal experiments [2, 3, 5, 8–10, 12, 13] and studies in patients with neurological disease [6, 7] and in normal anaesthetized humans [1, 11]. Species differences, intracerebral pathology and drug interactions may have had an important bearing on the results obtained.

The aims of our study were threefold: first, to identify the influence of nitrous oxide, second, to examine the effect of altering nitrous oxide concentrations and third, to compare the effects of large (60%) and small (30%) concentrations of nitrous oxide on CBF and transcranial Doppler ultrasound measurements (blood flow velocities in the right middle cerebral artery and the Pulsatility Index) in normal individuals.

SUBJECTS AND METHODS

After approval by the hospital's Ethics Committee, we studied 24 healthy male volunteers (mean age 28.5 yr, range 19–38 yr) with their informed consent. Each submitted to a routine clinical history, 12-lead ECG and haematological screen. In light of the known effects of nitrous oxide on haemopoiesis [14], the presence of an abnormal full blood count would have led to exclusion from the study. They were starved for 6 h before the study and requested not to smoke or consume caffeine-containing drinks for 12 h preceding the measurements, as both have been shown to affect CBF [15, 16].

Procedure

Three variables were examined in each volunteer: CBF was measured using the xenon-133 inhalation technique [17]; blood flow velocities, calculated from the time-averaged mean velocity (*V*tam) taken over the cardiac cycle in the right middle cerebral artery (MCA), were monitored using transcranial Doppler (TCD) ultrasound [18]; and the Pulsatility Index (PI)—defined as systolic velocity minus diastolic velocity divided by mean velocity—was calculated (Doptek Spectrascan with microcomputer) from the spectrally analysed pulse wave velocities obtained from the MCA. The inverse of this variable (1/PI) is theoretically proportional to flow [19]. *V*tam and PI were averaged over at least nine cardiac cycles to allow for normal variations, particularly respiratory variations. These variables were assessed with the following gas mixtures:

L. M. FIELD*, F.R.C.ANAES., E. K. KRZEMINSKA, F.R.C.ANAES., L. Z. BARSOUM, F.R.C.ANAES. (Department of Anaesthesia); D. E. DORRANCE, B.SC. (Department of Neurosurgery); Brook General Hospital, Shooters Hill Road, London SE18 4LW.
Accepted for Publication: August 20, 1992.

*Present address, for correspondence: Department of Anaesthesia, Kingston Hospital, Galsworthy Road, Kingston-Upon-Thames, Surrey KT2 7QB.

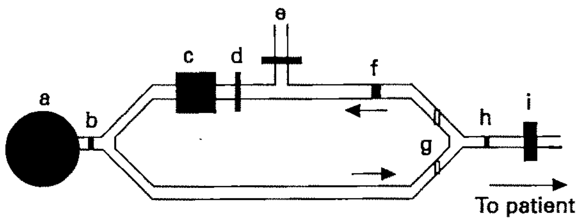


FIG. 1. Breathing circuit. a = 18-litre reservoir bag; b = fresh gas inlet; c = soda-lime canister; d = position of clamps for use as opened or closed circuit; e = scavenging limb; f = narrow limb for extraction of expired air; g = expiratory and inspiratory one-way valves; h = xenon-133 injection port; i = Oxicap gas sampler.

TABLE I. *Differences in CBF between 100% oxygen and 30% nitrous oxide (100–30), 100% oxygen and 60% nitrous oxide (100–60) and 30% nitrous oxide and 60% nitrous oxide (30–60).* **Difference significant* (P < *0.05*). *CL = Confidence limits*

	Differences in CBF (ml/100 g min^{-1})		
Subject No.	100–30	100–60	30–60
1	+11	+14	+3
2	+17	+8	−9
3	+2	0	−2
4	+17	+25	+8
5	−7	−20	−13
6	+4	+16	+12
7	+3	+5	+2
8	+10	+9	−1
9	+15	+5	−10
10	+3	+1	−2
11	+6	+22	+16
12	−10	+2	+12
13	+21	+20	−1
14	+4	+3	−1
15	+10	+30	+20
16	−3	−1	+2
17	+26	+10	−16
18	+36	+14	−22
19	−10	+11	+21
20	+17	+22	+5
Mean (SEM)	+8.6 (2.66)*	+9.8 (2.54)*	+1.2 (2.59)
95% CL	+3.39, +13.81	+4.82, +14.78	−3.88, +6.28

baseline 100% oxygen; 30% nitrous oxide in oxygen; 100% oxygen to confirm a return to baseline values; and 60% nitrous oxide in oxygen. Each subject acted as his own control. The sequence of gas mixtures was performed once in each volunteer.

The anaesthetic system used was a simple circle system (fig. 1); particular features comprised an 18-litre reservoir bag, an injection port for xenon-133 placed close to the subject and a small limb for extraction of expired air. An Air Force style mask was adjusted for comfort and secured by a harness to eliminate leaks. Each volunteer was allowed to familiarize himself with the circuit and mask before the first measurements were made.

The following procedure was adopted for each of the four measurements:

Step 1—A period of equilibrium for the appropriate gas mixture. During this time, the volunteer was allowed to breathe the gas mixture with the system exhausting to atmosphere. This took between 5 and 15 min, the first baseline run being the longest in order to allow for nitrogen washout as in any circle system.

Step 2—A period of equilibrium for xenon-133 within the system and the lungs. During this phase the system was closed to atmosphere and xenon-133 3 mCi was injected into the system. This phase lasted 2 min.

Step 3—A period of washout of xenon-133 from the cerebral hemispheres (detected by scintillation counters placed over the cranium) with the system exhausting to atmosphere; this phase lasted 2–3 min. CBF was calculated using three-dimensional deconvolutional analysis of the cerebral and lung (expired air) xenon-133 washout curves obtained as described by Wyper, Lennox and Rowan [17]. At the end of this period, the gas under study was cleared from the circuit and substituted by the next mixture to be examined.

On completion of this procedure, the volunteer was allowed to breathe 100% oxygen in order to aid recovery from the effects of 60% nitrous oxide.

Flow velocities in the MCA were monitored throughout the study (transcranial Doppler EME TC-2-64), the signals being recorded on magnetic tape. A 2-MHz pulsed Doppler transducer was placed on the skin surface just above the right zygomatic arch where the temporal bone is relatively thin, and the MCA insonated.

Other variables monitored continuously were: peripheral oxygen saturation (Sp_{O_2}), heart rate (HR), inspired oxygen concentration, end-tidal carbon dioxide $P\text{E}'_{CO_2}$ (Ohmeda OxiCap 4700) and non-invasive mean arterial pressure (MAP) (Nippon Corporation).

Comments made by the volunteers on the effects of nitrous oxide and observed effects of 30% and 60% nitrous oxide were recorded. All the results are expressed as the difference and the mean difference of the measurements obtained in order to compensate for age related variations in cerebral haemodynamics bearing in mind the 20-yr age range in our volunteers.

Statistical analysis

Data were analysed by Student's t test. The mean differences are reported with one SEM and $P < 0.05$ was taken as statistically significant. The 95% confidence limits on those means are also given. All calculations were made using Unistat III (Unisoft Ltd) on a Caf computer.

RESULTS

Of the 24 volunteers, 20 completed the study and four withdrew at various stages, for the following reasons: breathholding during the 60% nitrous oxide measurement, hysterical and uncontrollable laughter during the 60% nitrous oxide measurement, withdrawal of consent after distressing experiences caused by 30% nitrous oxide and severe abreaction during the 30% nitrous oxide measurement.

Comparison of 100% oxygen and 30% nitrous oxide, 100% oxygen and 60% nitrous oxide, and 30% and 60% nitrous oxide has given us differences and mean differences in CBF, *V*tam, 1/PI, HR, MAP and $P\text{E}'_{CO_2}$ (tables I–IV). Sp_{O_2} remained within

TABLE II. *Differences in* Vtam *between 100% oxygen and 30% nitrous oxide (100–30), 100% oxygen and 60% nitrous oxide (100–60) and 30% nitrous oxide and 60% nitrous oxide (30–60).* **Difference significant* (P < *0.05*). *CL = Confidence limits*

Subject No.	Difference in *V*tam (cm s^{-1})		
	100–30	100–60	30–60
1	+33.2	+50.8	+17.6
2	+13.6	+29.2	+15.6
3	+11.7	+21.4	+9.7
4	−1.9	+41.0	+42.9
5	+23.4	+37.0	+13.6
6	+9.7	+33.2	+23.5
7	+46.8	+27	−19.8
8	+2.0	+40.3	+38.3
9	+13.7	+29.3	+15.6
10	+23.4	+52.7	+29.3
11	+29.2	+50.7	+21.5
12	+11.7	+27.3	+15.6
13	+23.4	+17.6	−5.8
14	−1.9	+5.9	+7.8
15	+21.5	+25.4	+3.9
16	+15.6	+57.6	+42
17	+17.5	+48.7	+31.2
18	+11.7	+23.4	+11.7
19	+5.9	+21.5	+15.6
20	−5.8	+31.2	+37.0
Mean (SEM)	+15.22 (2.86)*	+33.56 (3.02)*	+18.34 (3.53)*
95% CL	+9.61, +20.83	+27.64, +39.48	+11.42, +25.26

TABLE III. *Differences in 1/PI between 100% oxygen and 30% nitrous oxide (100–30), 100% oxygen and 60% nitrous oxide (100–60) and 30% nitrous oxide and 60% nitrous oxide (30–60).* **Difference significant* (P < *0.05*). *CL = Confidence limits*

Subject No.	Difference in 1/PI		
	100–30	100–60	30–60
1	+0.32	+0.89	+0.57
2	+0.33	+0.33	0
3	+0.33	+0.83	+0.5
4	0	+0.42	+0.42
5	+0.42	+0.18	−0.24
6	+0.28	+0.42	+0.14
7	0	+0.42	+0.42
8	0	−0.14	−0.14
9	+0.32	+0.32	0
10	+0.42	+0.42	0
11	+0.42	+0.75	+0.33
12	−0.57	−0.33	+0.24
13	0	−0.24	−0.24
14	+0.14	0	−0.14
15	+0.42	0	−0.42
16	+0.32	+0.14	−0.18
17	+0.11	+0.67	+0.66
18	+0.18	+0.18	0
19	−0.2	+0.14	+0.34
20	−0.14	+0.18	+0.32
Mean (SEM)	+0.155 (0.058)*	+0.28 (0.075)	+0.124 (0.066)
95% CL	+0.041, +0.269	+0.133, +0.427	−0.005, +0.253

TABLE IV. *Mean differences in MAP, heart rate and* PE'_{CO_2} *between 100% oxygen and 30% nitrous oxide (100–30), 100% oxygen and 60% nitrous oxide (100–60), and 30% nitrous oxide and 60% nitrous oxide (30–60).* n = *20.* * *Difference significant* (P = *0.05*)

	Difference		
	100–30	100–60	30–60
MAP (mm Hg) Mean (SEM)	+0.75 (1.41)	+4.33 (2.3)	+3.6 (1.86)
95% CL	−2.01, +3.51	−0.18, +8.84	−0.05, +7.25
HR (beat min^{-1}) Mean (SEM)	−0.1 (0.86)	+5.15 (2.04)*	+5.25 (2.06)*
95% CL	−1.79, +1.59	+1.15, +9.15	+1.21, +9.29
PE'_{CO_2} (kPa) Mean (SEM)	−0.02 (0.10)	−0.06 (0.08)	−0.08 (0.06)
95% CL	−0.21, +0.17	−0.22, 0.10	−0.19, 0.03

the range 97–100% in all subjects. Analysis of data obtained for the 100% oxygen measurements used values recorded during the first baseline run. Comparison between the two 100% oxygen measurements showed no statistically significant difference in the variables examined (table V) confirming a return to normal baseline values after the 30% nitrous oxide measurement.

There was no significant change in MAP and *P*E'_{CO_2} during the study (table IV). Heart rate increased significantly with 60% nitrous oxide compared with 100% oxygen and 30% nitrous oxide, but not with 30% nitrous oxide compared with 100% oxygen (table IV). There were significant increases in CBF and 1/PI with 30% nitrous oxide compared with baseline. The increases with 60% nitrous oxide were not greater than those observed with 30% nitrous oxide (tables I, III). *V*tam increased significantly with 30% nitrous oxide compared with baseline followed by a further significant increases in this variable with 60% nitrous oxide (table II).

Of increasingly apparent interest during the course of the trial were the potent behavioural and psychological effects of nitrous oxide. Most enjoyed the experience, although some found it distressing. All volunteers were anxious, in spite of attempts to reduce the inevitable apprehension that participation in such a study would generate. All experienced amplification of sound. Thirteen of the remaining 20 volunteers dreamed with 60% nitrous oxide and one dreamed with both 30% and 60% nitrous oxide.

We have compared data from dreamers and non-dreamers, but care must be taken in interpreting this analysis, as poor recall of events was frequent and, of those who claimed not to have dreamed, several may simply not have remembered. Comparison was limited to the 60% nitrous oxide measurement as there was only one incidence of dreaming with 30%. In contrast with non-dreamers, CBF, *V*tam and 1/PI increased in all subjects who experienced dreams. Only the increase in 1/PI was statistically significant (table VI), although the 95% confidence limits suggest that, with greater numbers, the increase in CBF and *V*tam would also be significant.

DISCUSSION

We have shown that nitrous oxide administered in oxygen increased CBF in normal humans. A constant *P*E'_{CO_2} and, by implication, a constant arterial carbon dioxide tension, were maintained in the presence of good oxygenation and a stable arterial pressure and thus the known effects of hypercapnia, hypoxia and fluctuations in arterial pressure on cerebral haemodynamics were thereby excluded.

Anxiety is known to increase CBF [20] and all volunteers were apprehensive to a greater or lesser

TABLE V. *Mean* (SEM) *differences* [95% *confidence limits*] *in CBF*, V*tam*, *1/PI*, $P\acute{E}'_{CO_2}$, *HR and MAP between both measurements of 100% oxygen*. n = 20

CBF (ml/100 g min^{-1})	+3.85 (2.49)	[−1.03,+8.73]
*V*tam (cm s^{-1})	−3.05 (2.22)	[−7.40,+1.30]
1/PI	−0.25 (0.492)	[−0.12,+0.07]
$P\acute{E}'_{CO_2}$ (kPa)	+0.02 (0.10)	[−0.17,+0.21]
HR (beat min^{-1})	+0.4 (1.54)	[−2.12,+3.42]
MAP (mm Hg)	+0.13 (1.22)	[−2.26,+2.52]

TABLE VI. *Mean differences in CBF*, V*tam*, *1/PI*, $P\acute{E}'_{CO_2}$, *HR and MAP between dreamers and non-dreamers for 100% oxygen and 60% nitrous oxide*. n = 20. **Difference significant* (P < 0.05)

	100% O_2	60% N_2O
CBF (ml/100 g min^{-1})		
Mean (SEM)	+0.43 (1.82)	−4.60 (2.02)
95% CL	−3.13,+3.99	−8.55,−0.64
*V*tam (cm s^{-1})		
Mean (SEM)	+3.54 (2.15)	−16.59 (5.42)
95% CL	−0.76,+7.66	+5.95,+27.2
1/PI		
Mean (SEM)	+0.1 (0.06)	−0.27 (0.09)*
95% CL	−0.20,+0.22	−0.46,−0.07
$P\acute{E}'_{CO_2}$ (kPa)		
Mean (SEM)	−0.05 (0.09)	+0.07 (0.13)
95% CL	−0.23,+0.13	−0.19,+0.33
HR (beat min^{-1})		
Mean (SEM)	−3.62 (2.15)	+1.69 (2.35)
95% CL	−7.83,+0.59	−2.96,+6.29
MAP (mm Hg)		
Mean (SEM)	−4.6 (2.67)	−2.34 (2.02)
95% CL	−9.83,+0.63	−6.29,+1.61

degree. This was countered by using each subject as his own control. We do not believe that apprehension increased with inhalation of 30% nitrous oxide. The introduction of 60% nitrous oxide, however, coincided with a statistically significant increase in heart rate; this is explained most easily by increasing levels of anxiety. We cannot exclude this as having an influence on the results obtained. Dreaming is accompanied by a marked increase in mental activity and comparison between dreamers and non-dreamers suggests this may also have contributed, albeit insignificantly, to the observed increase in CBF caused by 60% nitrous oxide. When considering the influence of increasing anxiety and dreaming on cerebral haemodynamics, it is important to remember that the greatest changes occurred with 30% nitrous oxide when these factors were absent. Thus any contribution to the further insignificant increase observed with 60% nitrous oxide is unlikely to be important. Our results, interpreted with analysis of the spectrally analysed pulse wave velocities (fig. 2) suggest that vasodilatation was the immediate cause of increased CBF; this supports much of the available evidence [6, 21, 22]. However, we can only speculate on the mechanism by which nitrous oxide causes vasodilatation. A review of the literature leads us to support the theory that nitrous oxide acts predominantly by direct action on vascular smooth muscle or endothelium [22, 23]. The results of recent research into the properties of nitric oxide may shed some light on the mode of action of nitrous oxide. Nitric oxide is believed to be endothelium-derived relaxing factor (EDRF) [24], which is released from endothelial cells in response to stimulation by vasoactive substances. Synthesis of nitric oxide certainly appears to have an important influence on both basal tone and response of large cerebral arteries to acetylcholine *in vivo* [25]. Nitric oxide, in addition to other vasodilators such as nitroprusside and glyceryl trinitrate, facilitiates conversion of glyceryl triphosphate to cyclic glycerol monophosphate which leads to vascular smooth muscle relaxation [26]. There is no evidence to support the theory that nitric oxide and nitrous oxide have similar modes of action, but the possibility makes interesting speculation. Alternatively, nitrous oxide may cause vasodilatation indirectly by increasing the cerebral metabolic rate for oxygen ($CMRo_2$), although the evidence for this is conflicting [23]. Nitrous oxide has been shown to increase $CMRo_2$ markedly [10], moderately [9, 11] or not at all [3, 8], whilst consistently increasing CBF to a similar degree. Furthermore, in the isolated perfused brain preparation [22], cerebrovascular

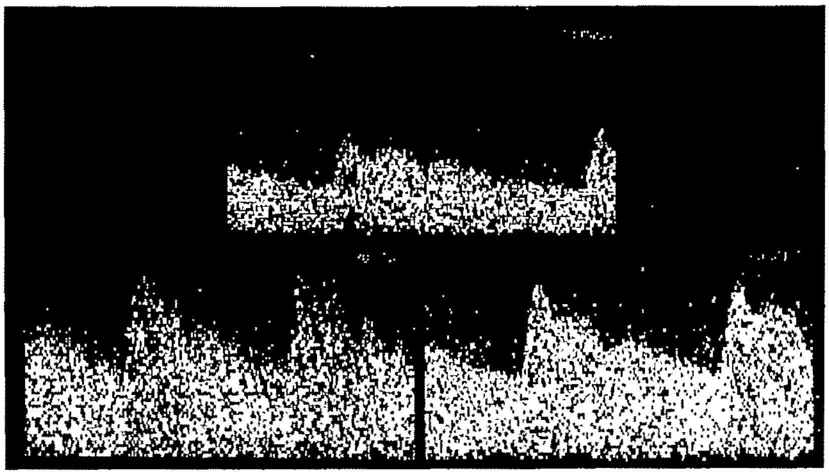


FIG. 2. MCA transcranial Doppler ultrasound waveforms showing changes in pulse wave velocities (*Y* axis) with time (*X* axis).

tone decreased significantly with CMRo$_2$ remaining unchanged. This suggests that, in the presence of nitrous oxide, changes in CBF are independent of changes in CMRo$_2$.

The most interesting aspect of our results is the existence of a plateau to the increase in CBF caused by nitrous oxide at or before a concentration of 30 %, confirmed with 1/PI. The only previous suggestion that nitrous oxide may have a biphasic effect came from Cole and Shapiro, who investigated the influence of increasing concentrations of nitrous oxide on cerebral and spinal cord glucose metabolism in the rat [27]. They found that, whereas 30 % nitrous oxide increased metabolism, 60 % nitrous oxide had the opposite effect. In this study, enflurane was administered concurrently with nitrous oxide in varying concentrations to maintain a constant MAC value and this may have affected the results. Whether we accept Cole and Shapiro's findings as having relevance to our study depends on whether we recognize a strong link between CBF and cerebral metabolism in the presence of nitrous oxide. We believe autoregulation of the small calibre vessels of the brain is the most likely explanation for the plateau described. This is supported by the fact that nitrous oxide does not affect autoregulative mechanisms [28]. However, the same assumption cannot be made of the large-calibre vessels. Unlike CBF, *V*tam increased steadily and significantly for both concentrations of nitrous oxide (the MCA monitored in our healthy volunteers is representative of a large calibre vessel). We believe the differences in CBF and *V*tam measurements lend further support to suggested differences in behaviour between the small and large calibre vessels of the brain. However, with indirect measurements, we are unable to support this theory.

Autoregulation has to be intact for the effects of nitrous oxide on CBF to be self-limiting. In those patients with intracerebral pathology in whom it is partially or totally abolished, there is evidence to suggest that nitrous oxide has a marked deleterious effect on cerebral haemodynamics [6]. Until recently, there have been no studies relating the use of nitrous oxide to neurological outcome. Baughman and colleagues examined this, together with neurohistopathological outcome, in rats subjected to incomplete cerebral ischaemia and given nitrous oxide alone, isoflurane alone or both agents in combination [29]. They found that nitrous oxide attenuated the cerebral protective effect of isoflurane and, when given alone, was associated with the worst prognosis.

There is increasing interest in the pulsatility index as a reliable indicator of cerebral perfusion, and its potential as a continuous non-invasive monitor is considerable. Our results confirm the relationship of 1/PI to CBF: both demonstrated the plateau we have described. Although 1/PI was not shown to increase significantly with 30 % nitrous oxide (this we believe was probably a reflection of the small number of subjects in our study), the overall trend was the same.

In conclusion, we believe two important facts have emerged from our study: first, nitrous oxide increases CBF. Second, the effect of nitrous oxide reaches a plateau at approximately 30 %. We suggest that intact autoregulation is the most likely explanation for this latter observation. In light of this, the use of nitrous oxide must be considered very carefully in patients with cerebral pathology in whom autoregulation is impaired.

REFERENCES

1. Wollman H, Alexander SC, Cohen PJ, Smith TC, Chase PE, van der Molen RA. Cerebral circulation during general anesthesia and hyperventilation in man. *Anesthesiology* 1965; **26**: 329–334.
2. Theye RA, Michenfelder JD. The effect of nitrous oxide on canine cerebral metabolism. *Anesthesiology* 1968; **29**: 1119–1124.
3. Carlsson C, Hagerdal M, Siesjo BK. The effect of nitrous oxide on oxygen consumption and blood flow in the cerebral cortex of the rat. *Acta Anaesthesiologica Scandinavica* 1976; **20**: 91–95.
4. Barker J. Nitrous oxide in neurosurgical anaesthesia. *British Journal of Anaesthesia* 1987; **59**: 146–147.
5. Archer DP, Labrecque P, Tyler JL, Meyer E, Trop D. Cerebral blood volume is increased in dogs during administration of nitrous oxide or isoflurane. *Anesthesiology* 1987; **67**: 642–648.
6. Henriksen HT, Balslev Jorgensen P. The effect of nitrous oxide on intracranial pressure in patients with intracranial disorders. *British Journal of Anaesthesia* 1973; **45**: 486–491.
7. Misfeldt BB, Balslev Jorgensen P, Rishoj M. The effect of nitrous oxide and halothane upon the intracranial pressure in hypocapnic patients with intracranial disorders. *British Journal of Anaesthesia* 1974; **46**: 853–858.
8. Kaieda R, Todd MM, Warner DS. The effects of anaesthetics and Pa_{CO_2} on the cerebrovascular, metabolic, and electroencephalographic responses to nitrous oxide in the rabbit. *Anesthesia and Analgesia* 1989; **68**: 135–143.
9. Sakabe T, Kuramoto T, Seiichiro I, Takeshita H. Cerebral effects of nitrous oxide in the dog. *Anesthesiology* 1978; **48**: 195–200.
10. Pelligrino DA, Miletich DJ, Hoffman WE, Albrecht RF. Nitrous oxide markedly increases cerebral cortical metabolic rate and blood flow in the goat. *Anesthesiology* 1984; **60**: 405–412.
11. Sakabe T, Kuramoto T, Kumagae S, Takeshita H. Cerebral responses to the addition of nitrous oxide to halothane in man. *British Journal of Anaesthesia* 1976; **48**: 957–961.
12. Seyde WC, Ellis JE, Longnecker DE. The addition of nitrous oxide to halothane decreases renal and splanchnic flow and increases cerebral blood flow in rats. *British Journal of Anaesthesia* 1986; **58**: 63–68.
13. Hansen TD, Warner DS, Todd MM, Vust LJ. Effects of nitrous oxide and volatile anaesthetics on cerebral blood flow. *British Journal of Anaesthesia* 1989; **63**: 290–295.
14. Nunn JF, Chanarin I. Nitrous oxide and vitamin B12. *British Journal of Anaesthesia* 1981; 50:1089–1090.
15. Dorrance DE, Bullock PR, Bagley JS, Neil Dwyer G. The response of intracranial vessels to cigarette smoking. In: Angerson WJ, Sheldon CD, Barbenel JC, Fisher AC, Gaylor GS, eds. *Blood Flow in the Brain*. Oxford: Oxford Science Publications, 1989; 88–94.
16. Matthew RJ, Wilson WH. Caffeine induces changes in cerebral circulation. *Stroke* 1985; **16**: 814–817.
17. Wyper DJ, Lennox GA, Rowan JO. Two minute slope inhalation technique for cerebral blood flow measurement in man. *Journal of Neurology, Neurosurgery and Psychiatry* 1976; **39**: 141–146.
18. Aaslid R, Markwalder TM, Nornes H. Non-invasive transcranial Doppler ultrasound recording of flow velocity in basal arteries. *Journal of Neurosurgery* 1982; **57**: 769–774.
19. Gosling RG, King DH. Processing arterial Doppler signals for clinical data. In: de Vleiger, ed. *Handbood of Clinical Ultrasound*, Chapter 60. New York: John Wiley and Sons, 1978; 613–646.
20. Kety SS. Discussion on psychoactive drugs and anxiety, their influence on cerebral circulation and metabolism. In: Ingvar DH, Lassen NA, eds. *Brain Work: the Coupling of Function,*

Metabolism and Blood Flow in the Brain. Copenhagen: Munksgaard, 1975; 472.

21. Laitinen LV, Johansson GG, Tarkkanen L. The effect of nitrous oxide on pulsatile cerebral impedence and cerebral blood flow. *British Journal of Anaesthesia* 1967; **39**: 781–785.
22. Fitzpatrick JH, Gilboe DD. Effects of nitrous oxide on the cerebrovascular tone, oxygen metabolism and electroencephalogram of the isolated perfused canine brain. *Anesthesiology* 1982; 57; 480–484.
23. Reasoner DK, Warner DS, Todd MM, McAllister A. Effects of nitrous oxide on cerebral metabolic rate in rats anaesthetized with isoflurane. *British Journal of Anaesthesia* 1990; **65**: 210–215.
24. Palmer RMJ, Ferrigo AG, Moncada S. Nitric oxide release accounts for the biological activity of endothelium-derived relaxing factor. *Nature (London)* 1987; **327**: 524–525.
25. Faraci FM, Heistad DD. Regulation of cerebral blood vessels by humoral and endothelium dependent mechanisms. Update on humoral regulation of vascular tone. *Hypertension* 1991; **17**: 917–922.
26. Brenner BM, Troy JL, Ballermann BJ. Endothelium-dependent vascular responses. *Journal of Clinical Investigation* 1989; **84**: 1373–1378.
27. Cole DJ, Shapiro HM. Different 1.2 MAC combinations of nitrous oxide–enflurane cause unique cerebral and spinal cord metabolic responses in the rat. *Anesthesiology* 1989; **70**: 787–792.
28. Smith AL, Neigh JL, Hoffman JC, Wollman H. Effects of general anesthesia on autoregulation of cerebral blood flow in man. *Journal of Applied Physiology* 1970; **29**: 665–669.
29. Baughman VL, Hoffman WE, Thomas C, Albrecht RF, Miletich DJ. The interaction of nitrous oxide and isoflurane with incomplete cerebral ischemia in the rat. *Anesthesiology* 1989; **70**: 767–774.

British Journal of Anaesthesia 1993; 70: 160–162

NEOSTIGMINE AND EDROPHONIUM ANTAGONISM OF MODERATE NEUROMUSCULAR BLOCK INDUCED BY PANCURONIUM OR TUBOCURARINE

G. D. SHORTEN, H. H. ALI AND N. G. GOUDSOUZIAN

SUMMARY

Edrophonium and neostigmine are anticholinesterase drugs used commonly to antagonize competitive neuromuscular block. Although it has a faster onset of action than neostigmine, edrophonium is unreliable when used to antagonize deep neuromuscular block. We have compared the antagonist characteristics of these two drugs when used to antagonize a moderate degree of pancuronium- or tubocurarine-induced neuromuscular block. Forty ASA I or II patients undergoing surgical procedures were allocated randomly to receive either pancuronium 70 μg kg^{-1} or tubocurarine 0.5 mg kg^{-1}, and to receive either edrophonium 0.5 mg kg^{-1} or neostigmine 0.05 mg kg^{-1}. Antagonism was attempted when the first response to train-of-four (TOF) stimulation recovered spontaneously to 25% of the control height. Neuromuscular function was monitored using the evoked integrated electromyogram of the first dorsal interosseous muscle of the hand. Adequate recovery was defined as the achievement of a TOF ratio of 0.70 or greater. Only seven of 20 patients who received edrophonium demonstrated adequate recovery 30 min after antagonism. Under the conditions described in this study, edrophonium 0.5 mg kg^{-1} was less effective as an antagonist than neostigmine 0.05 mg kg^{-1}. (Br. J. Anaesth. 1993; **70**: 160–162)

KEY WORDS

Antagonists, neuromuscular relaxants: edrophonium, neostigmine. Neuromuscular relaxants: pancuronium, tubocurarine.

The role of edrophonium in the antagonism of non-depolarizing neuromuscular block is uncertain. Its potential advantages include a faster onset of action (which, unlike neostigmine, makes it feasible to titrate dose to effect) and a lower requirement for anticholinergic drugs [1, 2]. In the presence of profound neuromuscular block (single twitch height < 10% of control height) these advantages appear to be offset by the inadequacy of the degree of recovery [3].

Intraoperative neuromuscular monitoring using a peripheral nerve stimulator is now widely practised and may be used reliably to differentiate between profound and moderate degrees of neuromuscular block. The effectiveness of edrophonium as an antagonist, when used at the lesser degree of neuromuscular block, is unclear. In order to examine this question, we attempted antagonism of a moderate degree of neuromuscular block (when the first response of TOF recovered spontaneously to 25% of the control height). Adequate antagonism was defined as the achievement of a train-of-four (TOF) ratio of 0.70 or greater. Our objective, therefore, was to compare edrophonium 0.5 mg kg^{-1} with neostigmine 0.05 mg kg^{-1} as antagonists of a moderate degree of neuromuscular block.

PATIENTS AND METHODS

After obtaining written informed consent and Institutional Ethics Committee approval, we studied 40 ASA I or II surgical patients undergoing elective surgery. Patients with neuromuscular disease or those receiving medication known to influence neuromuscular function were excluded.

Anaesthesia was induced with thiopentone 3–5 mg kg^{-1} and fentanyl 1–3 μg kg^{-1} and maintained with 66% nitrous oxide in oxygen, and increments of fentanyl, thiopentone, or both, as indicated clinically. Oral tracheal intubation was facilitated using pancuronium 70 μg kg^{-1} ($n = 20$) or tubocurarine 0.5 mg kg^{-1} ($n = 20$) according to random allocation.

The evoked integrated electromyogram (EMG) of the first dorsal interosseous muscle of the hand in response to supramaximal ulnar nerve TOF stimulation at 2 Hz was recorded and repeated once every 20 s using a Datex 221 NMT monitor. Two stimulating surface electrodes were placed over the ulnar nerve at the wrist and a sensing electrode placed over the belly of the first dorsal interosseous muscle with the reference electrode over the base of the proximal phalanx of the index finger. The ground electrode was placed at the wrist between the stimulating and recording electrodes. The monitored hand was immobilized in a fist-like position and enclosed in a plastic bag to minimize heat loss. An EMG control response was obtained after induction of anaesthesia when the eyelid reflex was abolished.

George D. Shorten, F.F.A.R.C.S.(I), F.R.C.Anaes.; Hassan H. Ali, M.D.; Nishan G. Goudsouzian, M.D.; Department of Anesthesia, Massachusetts General Hospital, Boston, MA 02114, U.S.A.
Accepted for Publication: July 24, 1992.
Correspondence to H. A. A.

When the first response of TOF recovered spontaneously to 25% of the control height, neuromuscular block was antagonized using either neostigmine 0.05 mg kg^{-1} or edrophonium 0.5 mg kg^{-1} according to random allocation.

The times from antagonism to recovery of first twitch height to 75% and 90% of the control value were measured, as were the TOF ratios corresponding to each of these levels of recovery. The times at which the TOF ratio reached 0.70 were also recorded if this occurred within 30 min of antagonism. Neuromuscular monitoring was discontinued either when the TOF ratio reached 0.70 or when 30 min had elapsed after antagonism.

The frequencies of adequate recovery were compared using two-tailed Fisher's exact test. Times to recovery of first twitch height to 75% and 90% of control and the corresponding TOF ratios were analysed using Friedman's analysis of variance (ANOVA on ranks) and Student's *t* test. $P < 0.05$ was taken to be significant.

RESULTS

The patient characteristics were similar in the four groups studied (table I). A Friedman ANOVA (ANOVA on ranks, table II) was performed to determine if differences existed between neuromuscular blockers, antagonists or interactions between the types of agent. This demonstrated a highly significant antagonist effect on the interval from antagonism to first twitch recovery to 75% and 90% ($P = 0.0001$ in each case). The rate of recovery of first twitch to 75% and 90% was significantly faster after endrophonium than after neostigmine ($P = 0.003$ and $P < 0.0001$ for 75% and 90% respectively) (table III) First twitch recovery to 75% of control occurred 1.3 min after antagonism with edrophonium and approximately 3.2 min after neostigmine. The corresponding intervals for recovery to 90% of control were approximately 1.5 min for edrophonium and 5 min for neostigmine.

TABLE I. *Patient characteristics (mean (range or* SD*))*

Group	Age (yr)	Sex (M:F)	Weight (kg)
Pancuronium–neostigmine	46.9 (22–79)	9:1	71.7 (11.6)
Pancuronium–edrophonium	46.3 (26–68)	8:2	67.7 (18.8)
Tubocurarine–neostigmine	35.4 (29–61)	7:3	68.3 (22.6)
Tubocurarine–edrophonium	44.2 (21–65)	9:1	70.3 (11.7)

TABLE II. *Results of Friedman ANOVA (ANOVA on ranks): the values shown represent the probability (P value) that a difference in the dependent variables is caused by the effect of a neuromuscular blocker, an antagonist, or their interaction. T75, T90 = Times from antagonism until first twitch response reached 75% and 90%, respectively, of control. TOF ratio at T1 75%, 90% = train-of-four ratio when first response to TOF stimulation is 75% and 90%, respectively, of control. Time to TOF ratio 0.70 = time from antagonism for train-of-four ratio to reach 0.70*

Dependent variable	Neuromuscular blocker	Antagonist	Interaction
T75	0.65	0.0001	0.79
T90	0.86	0.0001	0.76
TOF ratio			
at T1 75%	0.36	0.33	0.16
at T1 90%	0.10	0.44	0.01
Time to			
TOF ratio 0.70	0.17	0.14	0.38

TABLE III. *Mean (*SD*) times to single twitch recovery to 75% (T75) and 90% (T90)*

Group	T75	T90
Pancuronium–neostigmine	3.1 (1.9)	4.9 (2.0)
Pancuronium–edrophonium	1.3 (0.5)	1.5 (0.5)
Tubocurarine–neostigmine	3.2 (2.3)	5.3 (2.9)
Tubocurarine–edrophonium	1.3 (0.7)	1.7 (0.9)

TABLE IV. *Number of patients in each group in whom TOF ratio was greater than or equal to 0.70 30 min after antagonism*

Group	Total No. patients	No. with TOF ratio < 0.70
Pancuronium–neostigmine	10	10
Pancuronium–edrophonium	10	5
Tubocurarine–neostigmine	10	8
Tubocurarine–edrophonium	10	2
Neostigmine	20	18
Edrophonium	20	7

Irrespective of the neuromuscular blocking drug used, the frequency of adequate recovery was significantly greater after neostigmine than after edrophonium ($P = 0.0007$) (table IV). Only seven of the 20 patients who received edrophonium had TOF ratios greater than 0.70 at 30 min following antagonism (table IV). Two of 20 patients who received neostigmine exhibited inadequate antagonism with a TOF ratio less than 0.70 and both of these had received tubocurarine (table IV).

DISCUSSION

Our results indicate that, even when the depth of neuromuscular block is moderate and spontaneous recovery is well established, edrophonium 0.5 mg kg^{-1} is an unreliable antagonist of either pancuronium- or tubocurarine-induced neuromuscular block. Of 20 patients in whom antagonism was attempted using edrophonium, only seven demonstrated adequate recovery within 30 min. Eighteen of 20 patients in whom an equipotent dose of neostigmine was used demonstrated adequate recovery within 15 min. The insignificant *P* value (0.14), obtained using the ANOVA on ranks for antagonist effect on the time to reach a TOF ratio of 0.70 after antagonism is misleading. This occurred because patients who received edrophonium achieved TOF ratio = 0.70 either very rapidly or not at all (within the 30-min post-antagonism study period). Therefore, patients in the edrophonium group were ranked either very low or very high in terms of time to reach TOF ratio = 0.70, with a resultant cancelling effect.

Early investigations of edrophonium as an antagonist of non-depolarizing neuromuscular block indicated that it was unpredictable and that, because of its short duration of action, it was associated with recurarization [4]. When used to antagonize tubocurarine-induced neuromuscular block, edrophonium 10–20 mg initially produced a prompt increase in twitch height followed by a return of the recovery slope to pre-antagonism [5].

A subsequent investigation indicated that edrophonium, used in a larger bolus of 0.7 mg kg^{-1}, was an effective anticurare agent [6]. Independent work by Kopman [7] supported this finding, but emphasized the importance of the degree of neuromuscular block at which antagonism was attempted. It was concluded that, *provided four detectable responses to TOF stimulation were present*, edrophonium produced adequate and sustained recovery.

Reports followed to suggest the adequacy of edrophonium as an antagonist in a dose of 0.5 mg kg^{-1} or greater. Edrophonium 50–100 mg/70 kg was found to be effective in antagonizing pancuronium-induced neuromuscular block at 10 % recovery of muscle twitch [8]. At equiantagonistic doses, the duration of action of edrophonium was equal to that of neostigmine (0.5 mg kg^{-1} and 0.043 mg kg^{-1}, respectively) [1]. It was pointed out, however, that, as the dose–response curve of edrophonium was not parallel to those for neostigmine and pyridostimine, the relative potencies of the drugs would change with the degree of neuromuscular block at the time of administration. When neostigmine or edrophonium was used to antagonize atracurium-induced neuromuscular block of similar degree, adequate recovery (TOF ratio > 0.70) was demonstrable in all patients who received neostigmine 0.05 mg kg^{-1}, but in only 13 of 20 in whom edrophonium 0.5 mg kg^{-1} was used [9].

By 1986, it was apparent that edrophonium might be used successfully under certain circumstances only. Rupp and colleagues [10] compared edrophonium with neostigmine as antagonists of profound (single twitch $\leqslant 10\%$) and mild or moderate (single twitch $> 10\%$) neuromuscular block. These authors concluded that the dose equivalent to neostigmine 0.04 mg kg^{-1} was edrophonium 1.0 mg kg^{-1} for profound block and 0.5 mg kg^{-1} for mild or moderate block. The shortcomings of this work, however, have been noted previously, in particular the small doses of neuromuscular blockers used and the fact that adequacy of antagonism was determined as the point at which the single twitch recovered to 90 % of control [11]. The present study contradicts the findings of Rupp's groups that mild to moderate neuromuscular block was equally and effectively antagonized with both edrophonium 0.5 mg kg^{-1} and neostigmine 0.04 mg kg^{-1}. Although the dose of neostigmine in our study (50 µg kg^{-1}) was greater than that used by Rupp's group, we consider it unlikely that this difference accounts for the discrepancy in these results. We consider it more likely that the return of single twitch height to 90 % of control does not truly reflect adequate recovery.

Comparing edrophonium 0.5 mg kg^{-1} and neostigmine 0.04 mg kg^{-1} as antagonists of pancuronium-induced moderate neuromuscular block, Sanfilippo and colleagues [12] demonstrated that adequate antagonism using the former was inconsistent. However, these authors administered a smaller initial dose of pancuronium (0.05 mg kg^{-1}) after recovery from suxamethonium 1 mg kg^{-1}. Under these circumstances, a prolonged non-depolarizing block with pancuronium has been demonstrated [13]. We used a greater initial dose of pancuronium (70 µg kg^{-1}) to facilitate intubation in order to avoid this complicating factor.

Even when it is attempted to antagonize a moderate degree of neuromuscular block induced by pancuronium or tubocurarine, edrophonium 0.5 mg kg^{-1} is an inadequate antagonist. Thus we conclude that, in most situations, its relatively minor advantages are outweighed by this important factor.

REFERENCES

1. Cronnelly R, Morris RB, Miller RD. Edrophonium: duration of action and atropine requirements in humans during halothane anesthesia. *Anesthesiology* 1982; **57**: 261–266.
2. Dodd P, Day SJ, Goldhill DR, Macleod DM, Withington PS, Yale PM. Glycopyrronium requirements for antagonism of the muscarinic side effects of edrophonium. *British Journal of Anaesthesia* 1989; **62**: 77–81.
3. Power SJ, Jones RM. Reversal of profound paralysis: use of large doses of edrophonium to antagonize vecuronium and pancuronium induced neuromuscular blockade. *Acta Anaesthesiologica Scandinavica* 1989; **33**: 478–481.
4. Artusio JF, Riker WF, Wescoe WC. Studies of the interrelationships of certain cholinergic compounds. IV. Anti-curare action in anaesthetized man. *Journal of Experimental Pharmacology and Therapeutics* 1950; **100**: 227–237.
5. Katz RL. Neuromuscular effects of d-tubocurarine, edrophonium and neostigmine in man. *Anesthesiology* 1967; **28**: 327–336.
6. Bevan DR. Reversal of pancuronium with edrophonium. *Anesthesiology* 1979; **34**: 614–619.
7. Kopman AF. Edrophonium antagonism of pancuronium-induced neuromuscular blockade in man: A reappraisal. *Anesthesiology* 1979; **51**: 139–142.
8. Ferguson A, Egerszegi P, Bevan DR. Neostigmine, pyridostigmine, and edrophonium as antagonists of pancuronium. *Anesthesiology* 1980; **53**: 390–394.
9. Lavery GG, Mirakhur RK, Gibson FM. A comparison of edrophonium and neostigmine for the antagonism of atracurium induced neuromuscular blockade. *Anesthesia and Analgesia* 1985; **64**: 867–870.
10. Rupp SM, McChristian SW, Miller RD, Tabooda JF, Cronnelly R. Neostigmine and edrophonium antagonism of varying intensity neuromuscular blockade induced by atracurium, pancuronium or vecuronium. *Anesthesiology* 1986; **64**: 711–717.
11. Kopman AF. Recovery times following edrophonium and neostigmine reversal of pancuronium, atracurium and vecuronium steady-state infusions. *Anesthesiology* 1986; **65**: 572–573.
12. Sanfilippo M, Vilandi V, Fierro G, Rosa G, Pelaia P, Gaspanetto A. Neostigmine and edrophonium as antagonists of atracurium and pancuronium. *Acta Anaesthesiologica Scandinavica* 1988; **32**: 437–440.
13. Katz RL, Katz GJ. Clinical considerations in the use of muscle relaxants. In: Katz RL, ed. *Muscle Relaxants*. Amsterdam: North-Holland Publishing Co., 1975; 326.

British Journal of Anaesthesia 1993; 70: 163–166

TRACHEAL INTUBATION AFTER INDUCTION OF ANAESTHESIA WITH PROPOFOL, ALFENTANIL AND I.V. LIGNOCAINE

J. A. H. DAVIDSON AND J. A. GILLESPIE

SUMMARY

We have assessed tracheal intubating conditions in 60 ASA I or II patients after induction of anaesthesia with propofol 2.5 mg kg^{-1} and alfentanil 10 or 20 µg kg^{-1} with or without i.v. lignocaine 1 mg kg^{-1}. No neuromuscular blocking agents were administered. Patients were allocated randomly to four groups: group 1 = propofol–alfentanil 10 µg kg^{-1}; group 2 = propofol–alfentanil 10 µg kg^{-1}–lignocaine 1 mg kg^{-1}; group 3 = propofol–alfentanil 20 µg kg^{-1}; group 4 = propofol–alfentanil 20 µg kg^{-1}–lignocaine 1 mg kg^{-1}. Intubating conditions were assessed as acceptable or unacceptable on the basis of a scoring system dependent on ease of laryngoscopy, vocal cord position and coughing on insertion of the tracheal tube. Intubating conditions were acceptable in 20%, 73%, 73% and 93% of patients in groups 1–4, respectively. Intubating conditions were better and there was less coughing in the lignocaine group. (Br. J. Anaesth. 1993; **70**: 163–166)

KEY WORDS
Anaesthesia: intravenous. Intubation tracheal: technique.

Recent work has suggested that in premedicated patients an induction dose of propofol 2.5 mg kg^{-1} may provide adequate conditions for laryngoscopy and tracheal intubation without the need for neuromuscular blocking agents [1]. The efficacy of this single agent technique, however, has been debated [2], but in several individuals it is associated with sub-optimal conditions: undesirable haemodynamic responses, difficulty in seeing the larynx and intolerance of the tracheal tube.

It has been demonstrated that adjuvant agents, such as opioids, adrenergic blockers, and local anaesthetic agents, may suppress the cardiovascular response to laryngoscopy and tracheal intubation [3, 4] and improve tolerance of the tracheal tube. Although alfentanil and lignocaine have been shown to attenuate the cardiovascular response to intubation [5, 6], the effect of a combination of these drugs on intubating conditions remains poorly documented.

In this double-blind, randomized study, intubating conditions and haemodynamic response to intubation (in the absence of neuromuscular block) were assessed in patients induced with propofol 2.5 mg kg^{-1} and alfentanil 10 or 20 µg kg^{-1}. The effect of supplementing this regimen with i.v. lignocaine 1 mg kg^{-1} was evaluated.

PATIENTS AND METHODS

We studied 60 ASA I or II patients undergoing elective gynaecological surgery. Ethics Committee approval was obtained and each patient gave written informed consent. Patients whose physical characteristics suggested difficulties in intubation (Mallampati Class III) [7] and those who had a previously documented failed intubation were excluded from the study. All patients were premedicated with temazepam 20–30 mg approximately 1 h before anaesthesia. Patients were allocated randomly to one of four groups: group 1 = propofol 2.5 mg kg^{-1} and alfentanil 10 µg kg^{-1}; group 2 = propofol 2.5 mg kg^{-1}, alfentanil 10 µg kg^{-1} and i.v. lignocaine 1 mg kg^{-1}; group 3 = propofol 2.5 mg kg^{-1} and alfentanil 20 µg kg^{-1}; group 4 = propofol 2.5 mg kg^{-1}, alfentanil 20 µg kg^{-1} and i.v. lignocaine 1 mg kg^{-1}. Lignocaine and alfentanil were placed in 5-ml syringes and 0.9% saline was added to make a volume of 5 ml. Patients in groups 1 and 3 received saline 5 ml in place of lignocaine. Saline or lignocaine was administered 2 min and alfentanil 1 min before induction of anaesthesia with propofol. All injections were given over a period of 20 s. Laryngoscopy and intubation were attempted after loss of eyelash reflex (No. 3 Macintosh laryngoscope blade, 8.0-mm Portex tracheal tube). The study was performed in a double-blind fashion, the anaesthetist performing the intubation (J.A.H.D. or J.A.G.) being unaware of the group to which the patient had been allocated. Ease of intubation was assessed on the basis of the scoring system devised by Helbo-Hansen, Ravlo and Trap-Anderson [8]. Degree of coughing, position and movement of the vocal cords, and ease of laryngoscopy were estimated on a scale of 1–4 (table

---

J. A. H. DAVIDSON*, M.B., CH.B., F.R.C.ANAES., Clinical Shock Study Group, Department of Anaesthesia, Western Infirmary, Dumbarton Road, Glasgow G11 6NT. J. A. GILLESPIE, M.B., CH.B., F.R.C.ANAES., Department of Anaesthesia, Glasgow Royal Infirmary, Castle Street, Glasgow G4 0SF. Accepted for Publication: July 28, 1992.

*Present address, for correspondence: University Department of Anaesthesia, Glasgow Royal Infirmary, Castle Street, Glasgow G4 0SF.

TABLE I. *Intubating condition score*

	Score 1	 2	 3	 4
Laryngoscopy	Easy	Fair	Difficult	Impossible
Vocal cords	Open	Moving	Closing	Closed
Coughing	None	Slight	Moderate	Severe

TABLE II. *Patient data (mean (range or* SD*))*

	Group 1	Group 2	Group 3	Group 4
Age (yr)	32.4	29.7	30.9	31.87
	(24–46)	(24–38)	(24–40)	(25–38)
Weight (kg)	60.6	67.9	61.8	61.1
	(11.4)	(12.7)	(14.7)	(11.8)

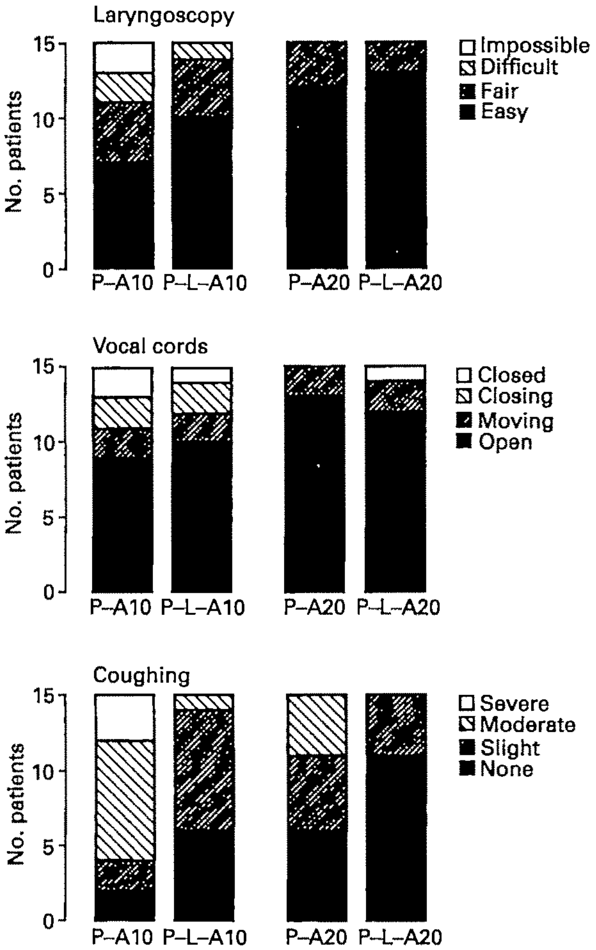


FIG. 1. Intubating condition score for laryngoscopy, vocal cords and coughing in patients from each group. P = Propofol; A10 = alfentanil 10 μg kg^{-1}; A20 = alfentanil 20 μg kg^{-1}; L = lignocaine.

I). Intubating conditions were judged acceptable when all scores were 2 or less. If any of the scores were 3 or 4, intubating conditions were judged unacceptable. Patients in whom intubation was impossible were given suxamethonium to optimize conditions.

After tracheal intubation, the lungs were ventilated with 67% nitrous oxide in oxygen 70 ml kg^{-1} min^{-1} (fresh gas flow) via a Mapleson D system, and after completion of the study period (2 min after intubation), inhalation agents were added to maintain anaesthesia.

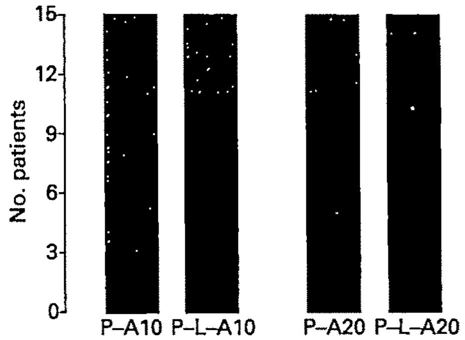


FIG. 2. Overall intubating conditions in patients from the four groups. All scores ≤ 2 = acceptable intubating conditions (■); any score > 2 = unacceptable intubating conditions (▨). P = Propofol; A10 = alfentanil 10 μg kg^{-1}; A20 = alfentanil 20 μg kg^{-1}; L = lignocaine.

Patients were monitored continuously by ECG and pulse oximetry. A baseline arterial pressure (Dinamap, Critikon) was measured before induction and was repeated immediately after both induction and intubation and thereafter at 1 and 2 min.

Statistics

The chi-square test and the Mann–Whitney *U* test were used for non-parametric data and the paired Student's *t* test and ANOVA for parametric data. The Bonferroni correction was used for inter- and intragroup comparisons. $P < 0.05$ was regarded as significant.

RESULTS

The four groups were comparable in age and weight (table II). There were no significant intergroup differences for baseline mean arterial pressure and heart rate. One patient commented spontaneously on tinnitus after injection of lignocaine. There was no other evidence of lignocaine toxicity.

Intubation was completed successfully in 56 of the 60 patients. In two patients in group 1, visualization of the larynx was impossible on laryngoscopy and in one patient from group 1 and one patient from group 2, the vocal cords were tightly closed, preventing intubation. After suxamethonium, intubation was achieved successfully in these four patients. Assessment of laryngoscopy, vocal cords and coughing are shown in figure 1. Vocal cord assessment was not greatly different between the four groups. Although ease of laryngoscopy improved with both the addition of i.v. lignocaine and the larger dose of alfentanil, the differences were not statistically significant. The incidence of coughing on insertion of the tracheal tube was reduced with lignocaine added to both the propofol–alfentanil 10 μg kg^{-1} ($P < 0.01$) and the propofol–alfentanil 20 μg kg^{-1} regimens.

The overall assessment of intubating conditions is shown in figure 2. Only three of 15 patients (20%) in group 1 were deemed to have satisfactory intubating conditions, compared with 11 of 15 patients (73%) in groups 2 and 3 and 14 of 15 patients (93%) in group 4. There was a statistically significant dif-

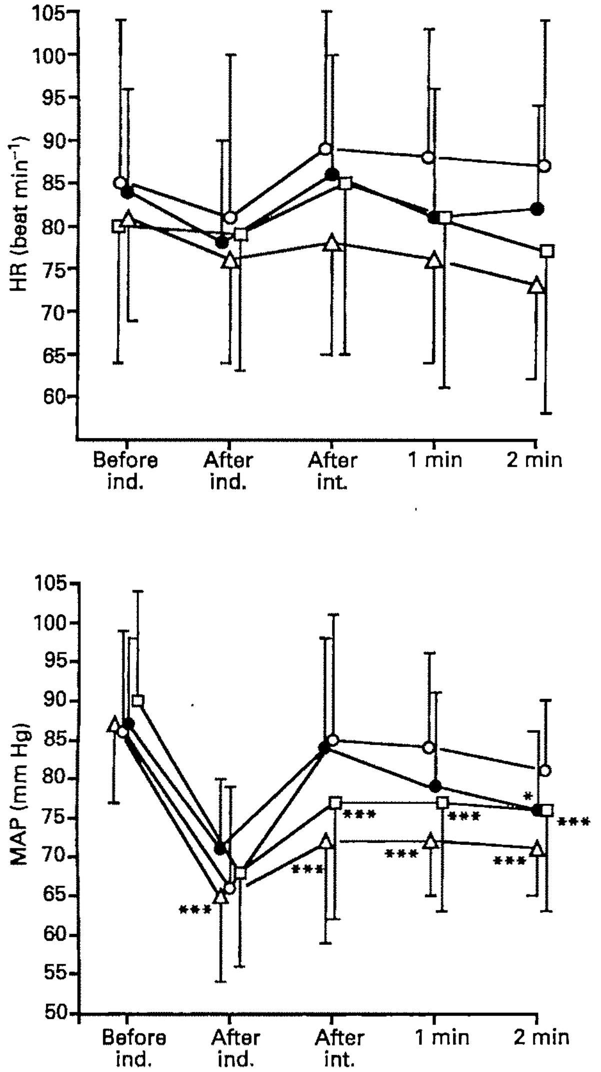


FIG. 3. Cardiovascular (heart rate (HR) and arterial pressure (MAP)) responses to laryngoscopy and intubation in the propofol–alfentanil 10 $\mu g\ kg^{-1}$ (○), propofol–alfentanil 10 $\mu g\ kg^{-1}$ with lignocaine (●), propofol–alfentanil 20 $\mu g\ kg^{-1}$ (□) and propofol–alfentanil 20 $\mu g\ kg^{-1}$ with lignocaine (△) groups. Within group statistically significant changes compared with the value before induction: *$P < 0.05$; ***$P < 0.001$. ind. = induction; int. = intubation.

ference ($P < 0.05$) between overall intubating conditions in group 1 (propofol–alfentanil 10 $\mu g\ kg^{-1}$) and group 3 (propofol–alfentanil 20 $\mu g\ kg^{-1}$). Addition of lignocaine to propofol–alfentanil 10 $\mu g\ kg^{-1}$ resulted in an improvement in intubating conditions ($P < 0.05$). Similarly, supplementing propofol–alfentanil 20 $\mu g\ kg^{-1}$ with lignocaine improved intubating conditions, although this did not achieve statistical significance.

Cardiovascular responses to induction and intubation are shown in figure 3. Heart rate decreased after induction and increased after intubation in all groups. However, none of the changes was statistically significant compared with baseline values. Similarly, mean arterial pressure decreased in all groups after induction ($P < 0.001$). However, there was an increase in all groups after intubation, but the mean arterial pressure remained depressed in groups 3 and 4 compared with pre-induction values ($P < 0.005$ and $P < 0.001$, respectively).

DISCUSSION

Several studies have concluded that intubation is possible without the use of neuromuscular blocking agents. Lewis demonstrated in 1948 that adequate conditions for intubation could be achieved using thiopentone alone [9]. McKeating and colleagues [10] found that, when no neuromuscular blocking drugs were given, laryngoscopy was possible significantly more often after propofol than after thiopentone. Conditions, however, are not always optimal. Keavney [1], using only propofol 2.5 mg kg^{-1}, reported satisfactory intubating conditions in 12 of 20 patients (60 %), whereas Saarnivaara and Klemola [2], using a similar regimen, reported that only five of 13 patients (38 %) had intubating conditions that were adequate. Even after administration of alfentanil 20 $\mu g\ kg^{-1}$ 30 s before induction, in only 10 of 15 patients (66 %) were intubating conditions deemed to have been adequate [2].

In this study, we have demonstrated that the use of i.v. lignocaine to supplement propofol–alfentanil anaesthesia improved intubating conditions. Lignocaine 1 mg kg^{-1} i.v., when administered 2 min before induction with propofol–alfentanil 10 $\mu g\ kg^{-1}$, increased the number of patients with acceptable intubating conditions from three of 15 (20 %) to 11 of 15 (79 %) ($P < 0.05$). The improvement in intubating conditions was largely caused by a reduction in the incidence and severity of coughing after insertion of the tracheal tube, although an improvement in the ease of laryngoscopy was also apparent.

There are many reports on the antitussive effects of i.v. lignocaine [11–13]. Lignocaine has also been shown to attenuate the increase in heart rate [13], arterial pressure [14] and intracranial pressure [15] associated with laryngoscopy and intubation. The mechanism whereby i.v. lignocaine suppresses the cough reflex is still unclear, but the efficacy has been shown to increase in a dose-dependent manner, and correlates well with plasma concentrations [13]. Yukioka and colleagues demonstrated that administration of lignocaine 2 mg kg^{-1} was effective in blocking the cough reflex during intubation in patients in whom anaesthesia was induced and maintained with nitrous oxide and halothane in oxygen, coughing being effectively eliminated by plasma concentrations of lignocaine in excess of 3 $\mu g\ ml^{-1}$ [13]. It was planned initially to use a 2-mg kg^{-1} dose of i.v. lignocaine in this study; however, after a small pilot study in which five of six patients complained spontaneously of tinnitus, circumoral paraesthesia and dizziness, the dose was reduced to 1 mg kg^{-1}. This dose significantly reduces the incidence of coughing [13] and, as we have demonstrated, was associated with minimal side effects.

It is likely that the antitussive effect of lignocaine is caused at least partially by an increase in the depth of general anaesthesia. Indeed, blood concentrations of 3–6 $\mu g\ ml^{-1}$ are known to potentiate the effects of nitrous oxide anaesthesia with a 10–28 % reduction in the minimum alveolar concentration (MAC) of halothane [16].

REFERENCES

1. Keaveny JP, Knell PJ. Intubation under induction doses of propofol. *Anaesthesia* 1988; 43S: 80–81.
2. Saarnivaara L, Klemola UM. Injection pain, intubating conditions and cardiovascular changes following induction of anaesthesia with propofol alone or in combination with alfentanil. *Acta Anaesthesiologica Scandinavica* 1991; **35**: 19–23.
3. Bedford RF, Marshall WK. Cardiovascular responses to endotracheal intubation during four anaesthetic techniques. *Acta Anaesthesiologica Scandinavica* 1984; **28**: 563–566.
4. Ebert JP, Pearson JD, Gelman S, Harris C, Bradley EL. Circulatory responses to laryngoscopy: the comparative effects of placebo, fentanyl and esmolol. *Canadian Journal of Anaesthesia* 1989; **36**: 301–306.
5. Black TE, Kay B, Healy TEJ. Reducing the haemodynamic responses to laryngoscopy and intubation. *Anaesthesia* 1984; **39**: 883–887.
6. Abou-Madi MN, Keszler H, Yacoub JM. Cardiovascular reactions to laryngoscopy and intubation following small and large intravenous doses of lidocaine. *Canadian Anaesthetists Society Journal* 1977; **24**: 12–19.
7. Mallampatti SR, Gatt SP, Gugino LD, Desai SP, Waraksa B, Freiberger D, Liu PL. A clinical sign to predict difficult tracheal intubation: a prospective study. *Canadian Anaesthetists Society Journal* 1985; **32**: 429–434.
8. Helbo-Hansen S, Ravlo O, Trap-Anderson S. The influence of alfentanil on the intubating conditions after priming with vecuronium. *Acta Anaesthesiologica Scandinavica* 1988; **32**: 41–44.
9. Lewis CB. Endotracheal intubation under thiopentone. *Anaesthesia* 1948; **3**: 113–115.
10. McKeating K, Bali IM, Dundee JW. The effects of thiopentone and propofol on upper airway integrity. *Anaesthesia* 1988; **43**: 638–640.
11. Stenhause JE, Gaskin L. A study of intravenous lidocaine as a suppressant of cough reflex. *Anesthesiology* 1963; **24**: 285–290.
12. Poulton TJ, James FM. Cough suppression by lidocaine. *Anesthesiology* 1979; **50**: 470–472.
13. Yukioka H, Yoshimoto N, Nishimura K, Fujimori M. Intravenous lidocaine as a suppressant of coughing during tracheal intubation. *Anesthesia and Analgesia* 1985; **64**: 1189–1192.
14. Abou-Madi MN, Keszler H, Yacoub JM. Cardiovascular reactions to laryngoscopy and tracheal intubation following small and large intravenous doses of lidocaine. *Canadian Anaesthetists Society Journal* 1977; **24**: 2–19.
15. Hammill JF, Bedford RF, Weaver DC, Colohan AR. Lidocaine before endotracheal intubation: Intravenous or laryngotracheal? *Anesthesiology* 1981; **55**: 578–581.
16. Himes RS, DiFazio CH, Burney RG. Effects of lidocaine on the anesthetic requirements for nitrous oxide and halothane. *Anesthesiology* 1977; **47**: 437–440.

British Journal of Anaesthesia 1993; **70**: 167–172

EFFECTS OF INTRADERMAL LIGNOCAINE AND MEPIVACAINE ON HUMAN CUTANEOUS CIRCULATION IN AREAS WITH HISTAMINE-INDUCED NEUROGENIC INFLAMMATION

H. FRUHSTORFER AND G. WAGENER

SUMMARY

The vasoconstrictive potencies of lignocaine and mepivacaine were studied in human skin. Lignocaine 0.5%, 0.25% mepivacaine (both plain and mixed with adrenaline or ornipressin), and saline (control) were injected intradermally into skin areas with enhanced perfusion (1% histamine prick). Flux was determined by scanning laser Doppler flowmetry and the size of any eventual pallor was measured. The artificially enhanced flux was increased further by saline, but not altered by the local anaesthetics. Mepivacaine produced a small pallor. Both vasoconstrictors reduced flux significantly and produced a larger pallor. We conclude that both local anaesthetics have only a mild constrictive effect on precapillary vessels. Mepivacaine has, additionally, a constrictor effect on the postcapillary vascular bed, causing pallor. An effective precapillary constriction which reduces the capillary clearance of both local anaesthetics can be achieved only by addition of a vasoconstrictor. (Br. J. Anaesth. 1993; **70**: 167–172)

KEY WORDS

Anaesthetics, local: lignocaine, mepivacaine, vasoactivity. Skin: dermal blood flow.

Most modern local anaesthetics appear to be vasodilatators in clinical concentrations and vasoconstrictor agents such as catecholamines or vasopressin derivatives are usually added. The same local anaesthetics in small concentrations, however, apparently constrict vessels [1].

The vasoactive properties of local anaesthetics have been examined by many different experimental approaches. Methods to estimate cutaneous circulation in human skin include visual inspection of colour changes [2–5], thermal clearance [6] and laser Doppler flowmetry [7, 8]. Results are generally inconsistent and difficult to interpret.

Although the skin is easily accessible for examination of vasoactivity of drugs, it presents several difficulties for the interpretation of the results. First, at rest, capillary perfusion of the skin is so low that vasoconstrictor effects are difficult to detect [8]. Furthermore, even a minute injury such as the insertion of a fine needle [7, 9] or the injection of a small quantity of saline [7, 9] produces a rapid and marked increase in blood flow within a radius of up to several centimetres. This is caused by release of vasoactive substances (peptides, histamine) from stimulated nociceptors and mastcells (neurogenic inflammation; see [10] for a review). Consequently, the injection of a vasoconstrictive agent produces both dilatation and constriction in unpredictable proportions. For example, the intracutaneous (i.c.) injection of ropivacaine in a concentration thought to cause vasoconstriction enhances cutaneous perfusion, although the flux increase is less pronounced than that caused by saline [7].

In an attempt to find a stable and reproducible condition in which vasoconstriction can be measured, cutaneous vasodilatation induced by local heating has been used [8]. In this condition, the s.c. injection of 0.5% lignocaine causes a significant reduction in cutaneous blood flow, which is reduced further if adrenaline or ornipressin is added [8]. However, this does not pertain during regional anaesthesia, in which tissue is not heated, but rather stimulated by mechanical trauma and chemical irritation. Therefore a stable neurogenic inflammation of the skin seems to be a more natural condition to test local anaesthetics.

We have examined the vasoactive properties of 0.5% lignocaine and 0.25% racemic mepivacaine in skin areas with neurogenic inflammation induced by histamine. In these concentrations, lignocaine is thought to have vasodilator and mepivacaine vasoconstrictor properties [11]. Both drugs were used plain and in combination with adrenaline or ornipressin, and they were compared with saline as control. The induced changes in cutaneous circulation were determined by scanning laser Doppler flowmetry [12] and by the measurement of pallor and flare areas.

SUBJECTS AND METHODS

The following drugs were used: saline (0.9% NaCl, Braun Melsungen); lignocaine (0.5% Xylocain, Astra); mepivacaine (0.5% Scandicain, Astra); ornipressin (Por 8, Sandoz); adrenaline (Suprarenin 1:1000, Hoechst); histamine (1% histamine hydro-

---

H. Fruhstorfer, M.D.; G. Wagener, M.D.; Institute of Physiology, University of Marburg, Deutschhausstr.1–2, D-3550 Marburg, Germany. Accepted for Publication: July 2, 1992.

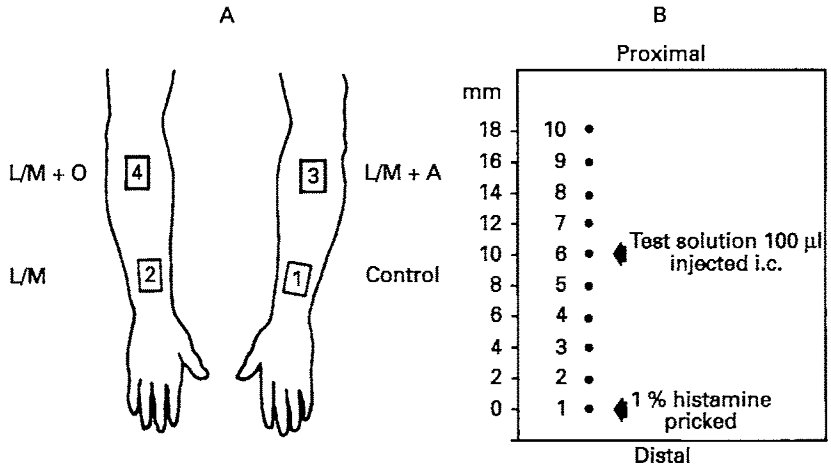


FIG. 1. A: Position of the four test areas on the dorsal forearms. Numbers give the order of testing. L = Lignocaine; M = mepivacaine. B: Position of the 10 measurement points and the points of histamine prick and of test solution injection. At each of the 10 points, flux was measured at a rate of 1 per 25 s. Each flux value represents the average of four consecutive measurements during 2 s.

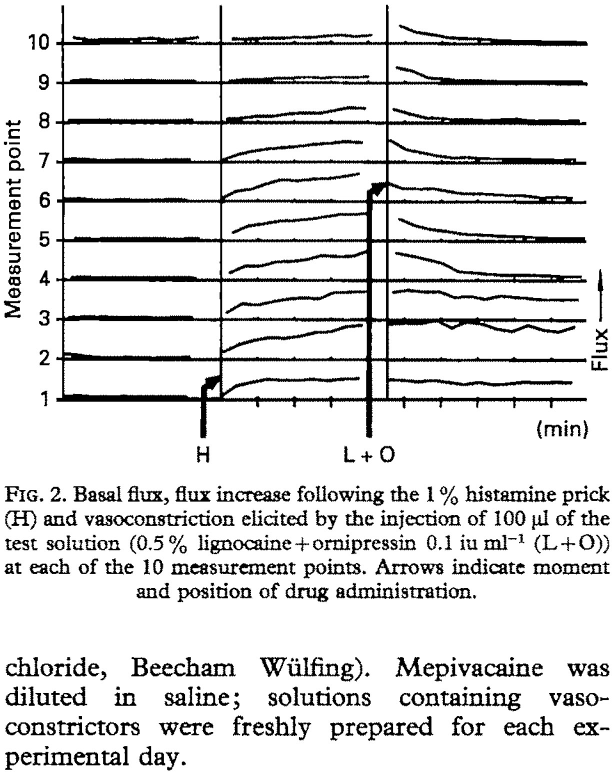


FIG. 2. Basal flux, flux increase following the 1 % histamine prick (H) and vasoconstriction elicited by the injection of 100 µl of the test solution (0.5 % lignocaine + ornipressin 0.1 iu ml^{-1} (L + O)) at each of the 10 measurement points. Arrows indicate moment and position of drug administration.

chloride, Beecham Wülfing). Mepivacaine was diluted in saline; solutions containing vasoconstrictors were freshly prepared for each experimental day.

We studied 24 healthy volunteers (10 male) (mean age 25.6 yr, range 22–32 yr) who had given informed consent. In 12 subjects, lignocaine was examined; this group received saline (control), plain 0.5 % lignocaine (L), 0.5 % lignocaine with adrenaline 5 µg ml^{-1} (L + A) and 0.5 % lignocaine with ornipressin 0.1 iu ml^{-1} (L + O). In the other group ($n = 12$), mepivacaine was examined: saline (control), plain 0.25 % mepivacaine (M), 0.25 % mepivacaine with adrenaline 5 µg ml^{-1} (M + A) and 0.25 % mepivacaine with ornipressin 0.1 iu ml^{-1} (M + O).

Neurogenic inflammation was elicited by pricking 1 % histamine into the skin. Cutaneous perfusion was monitored by a two-channel laser Doppler flowmeter (Moore Instruments MFD3) combined with an automatic scanning device [12]. The approximate area of flare was estimated by measuring its long and short axes and calculating the area of an ellipse. The outline of a pallor was transferred to transparent film and its area determined by weighing the cutting.

Before an experiment, four test areas were selected on both dorsal forearms (fig. 1A); the test areas were not randomized as, in this region, basal capillary perfusion and the response to histamine are comparable. The scanning device was fixed to the area by double adhesive tape and flux was measured at a rate of one per 25 s at each of 10 points 2 mm apart (fig. 1B). After baseline flux had been recorded for 3 min, histamine was pricked at point 1. Flux recording was continued for another 3 min to allow development of neurogenic inflammation. Then 100 µl of the test solution was injected i.c. with a 26-gauge needle at point 6 (fig. 2). The depth of the injection was selected carefully to be as shallow as possible, but deep enough to avoid the development of a pale papule. After the injection, the recording was continued for another 5 min, then the axes of the flare were measured and the size of any eventual pallor was transferred to transparent film. After another 5 min, the final size of the pallor was recorded. All flux data were collected continuously by computer.

After an experiment, basal flux values, maximal flux after histamine prick and maximal deviation from histamine flux during the 5 min after injection of the test substances were determined for each measurement point. Maximal flux changes elicited by the administration of histamine or the test solutions were expressed as per cent of basal flux (= 100 %). In addition, the latencies of 50 % maximal flux reduction were determined for the solutions containing additives. For statistical analysis, the flux values at measurement point 4 were selected, because at this point neurogenic inflammation and the vasoconstrictor effects of the drugs combine without being disturbed by the tissue pressure of the histamine weal or of the injection. For each group, differences between histamine-enhanced flux and drug-induced flux responses and the differences in the size of pallors were tested by the Wilcoxon signed rank test for paired replicates. In order to

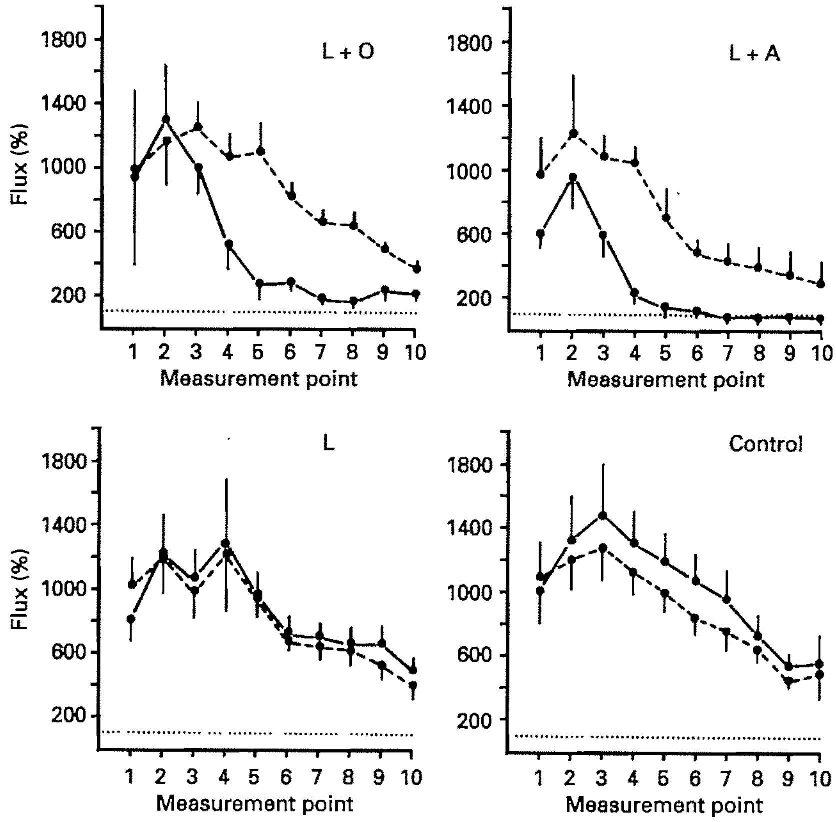


FIG. 3. Lignocaine results. Average maximal flux following histamine prick (——) and average maximal deviation from histamine flux during the 5 min following the injection of the test solutions (– – –). The data are given for each of the 10 measurement points in percent of basal flux (= 100 %, dotted line). Bars give SE to one side. Small flux values at point 1 are caused by the histamine weal. L = Lignocaine; O = ornipressin; A = adrenaline.

maintain an overall 5 % level of significance, the limits within the single tests were adjusted according to Bonferroni–Holm.

RESULTS

In all subjects, histamine caused a rapid increase in cutaneous perfusion which, on average, was more than 10-fold baseline flux near the prick; at increasing distance from the prick, flux values decreased and reached about four times baseline at point 10 (figs 2–4). There were great interindividual variations in the reactivity to histamine. The average flare size was 6.94 (SD 2.54) cm^2 in group L and 7.22 (2.22) cm^2 in group M. In both groups, the injection of saline produced a further statistically significant increase in perfusion (figs 3, 4). The injection of plain lignocaine caused a slight increase in perfusion in 11 of the 12 test subjects; no colour changes of the skin around the injection occurred. Plain mepivacaine did not change perfusion between the histamine prick and the injection; in the periphery of neurogenic inflammation, 10 of the 12 subjects produced a small flux reduction. Nine subjects developed a distinct pallor around the mepivacaine injection (fig. 5). Both adrenaline and ornipressin, when added to the local anaesthetic, caused a decrease in skin perfusion (statistically significant for L+A, L+O and M+A) which reached baseline values around the injection (figs 3, 4). In both groups, the flux decrease tended to develop more rapidly with adrenaline than with ornipressin (fig. 6) and it was accompanied by a marked pallor. Five minutes after the injection, the pallor had reached almost its final size, which was the same for adrenaline and ornipressin, when added to lignocaine; however, when added to mepivacaine, ornipressin produced, in all cases, a smaller pallor (fig. 5). The pallor produced by plain mepivacaine was in all cases smaller than that elicited by the two vasoconstrictors.

DISCUSSION

Histamine-induced neurogenic inflammation of the skin has proved to be a good experimental method for studying vasoactive properties of local anaesthetics. It provides a stable condition of enhanced blood flow lasting up to 1 h and allows observation of both vasodilatation and vasoconstriction. The vascular effects of small quantities of local anaesthetics, when injected into the skin with artificially enhanced blood flow, result from three separate mechanisms: the initial mechanical trauma and chemical irritation stimulate nociceptors and cause additional vasodilatation; the local anaesthetic blocks sympathetic axons and reduces the thermoregulatory vasoconstrictor tone (true for hands and feet); the local anaesthetic has intrinsic effects on vascular smooth muscle, either direct or through mediators.

Assuming that the injection of saline causes only neurogenic inflammation, a local anaesthetic without intrinsic vasoactivity should cause a comparable increase in blood flow. In this study, 0.5 % lignocaine increased flux less than saline and 0.25 %

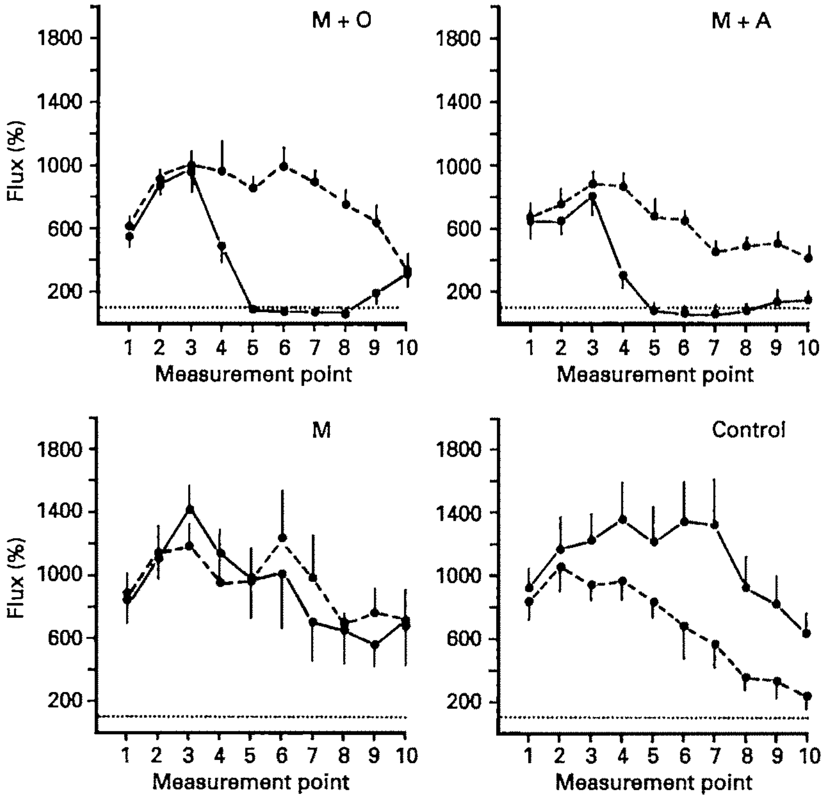


FIG. 4. Mepivacaine results. Average maximal flux following histamine prick (——) and average maximal deviation from histamine flux during the 5 min following the injection of the test solutions (——). The data are given for each of the 10 measurement points in percent of basal flux (= 100 %, dotted line). Bars give SE to one side. Small flux values at point 1 are caused by the histamine weal. M = Mepivacaine; O = ornipressin; A = adrenaline.

mepivacaine even tended to reduce flux in the periphery of neurogenic inflammation. This indicates that both local anaesthetics in the concentrations used have a mild intrinsic constrictor effect on the precapillary side of human skin circulation. A decrease in cutaneous blood flow caused by s.c. 0.5 % lignocaine has been observed earlier in a study with heat-induced vasodilatation [8]. Mesnil du Rochemont and Hensel [6], using a thermal clearance method with intradermal injection of 1 % lignocaine or 1 % mepivacaine, found a reduction in flow following an initial increase of about 20 min duration (probably the effect of the injection trauma). Other studies using laser Doppler flowmetry found, in comparison with saline, larger flux increases with 1 % lignocaine [7, 11]; conversely 0.5 % mepivacaine produced smaller flux increases [11].

Although we found that 0.5 % lignocaine and 0.25 % mepivacaine did not alter artificially enhanced perfusion to a significant extent, both drugs differed in one important aspect: in the majority of cases, mepivacaine produced a small pallor whereas lignocaine did not. This is puzzling, because flux in the pallor area was still considerably enhanced and it was far from the baseline values which were reached when vasoconstrictors were

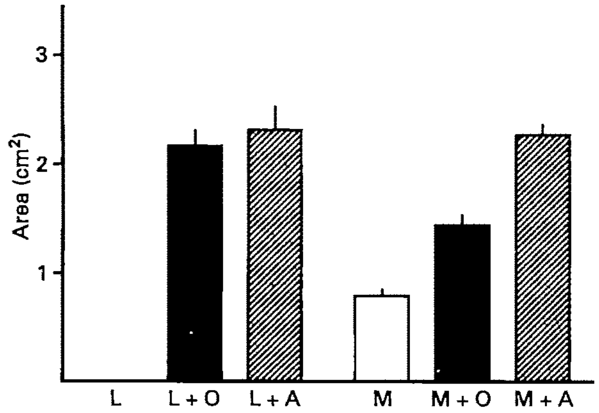


FIG. 5. Average area of pallors 10 min after the injection of the test solutions. Bars give SE to one side. L = Lignocaine; O = ornipressin; A = adrenaline; M = mepivacaine.

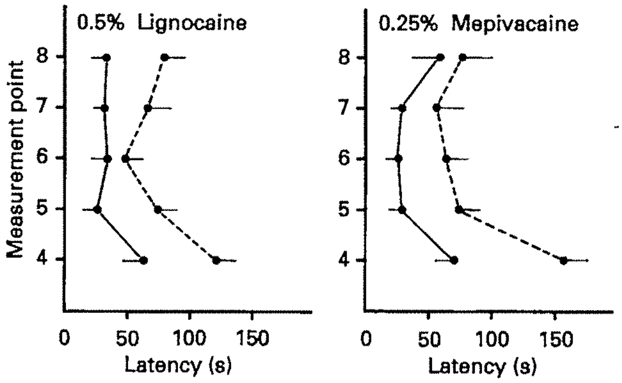


FIG. 6. Average latency of 50 % flux reduction following the injection of the test solutions containing adrenaline (——) or ornipressin (——) at measurement points 4 to 8. Bars give SE to one side.

added. The dissociation between flux and colour is probably caused by the fact that the flowmeter measures the volume of blood per minute passing through the vertically arranged capillary loops, whereas skin colour is determined mainly by the volume of blood present within the deeper horizontal networks of the venous plexus. If a drug has a differential effect on precapillary and postcapillary vessels, a large flux in a pale skin could result. Therefore it is possible that 0.25% mepivacaine has a stronger constrictive effect on venules and veins than on arterioles and precapillary sphincters. When a small concentration of mepivacaine is injected into untreated skin, trauma-elicited neurogenic inflammation overcomes the mild constrictor action on precapillary vessels, leading to a flux increase [6, 11]. Simultaneously, in the postcapillary vascular bed, vasoconstriction prevails; the resulting pallor has been observed in several studies [3, 5]. In this study, no pallor was observed with 0.5% lignocaine, indicating that the constrictor effect on the postcapillary vessels was less marked. A differential effect on the arterial and venous vascular beds has also been observed when lignocaine and mepivacaine were infused into the brachial artery of human volunteers [13]: no direct effects on vascular resistance occurred, whereas venous tone was increased markedly. The differential effects of mepivacaine on arterial and venous vascular beds could be explained by the existence of two different routes of action. When injected in small concentrations into the extracellular space, the local anaesthetic penetrates the adventitia and has a direct constrictor effect on vascular smooth muscle. At the same time, the local anaesthetic is leaking through the capillary walls and drains away through venules and veins of the venular plexus. There, it could exert an additional indirect effect on venous smooth muscle mediated by the endothelium; it could either stimulate the release of endothelins or inhibit the release of endothelium-derived relaxing factor (EDRF). In man, the i.a. injection of an inhibitor of EDRF synthesis reduces arterial flow [14], but the i.v. injection does not by itself have a venoconstrictor effect [15]. In contrast, the intradermal injection of endothelin 1 causes a reduction in cutaneous perfusion, together with a small pallor [16]. Therefore, it could be that mepivacaine stimulates the endothelium to release endothelins. However, the absence of an increase in vascular resistance during i.a. infusion of mepivacaine when the sympathetic system is blocked [13] does not support a simple endothelium-mediated action of local anaesthetics.

When added to 0.5% lignocaine, both adrenaline and ornipressin caused a rapid decrease in flux to baseline values and they produced a pallor of comparable size. In combination with 0.25% mepivacaine, both vasoconstrictors produced a similar rapid flux decrease; ornipressin, however, produced a significantly smaller pallor. A similar difference could not be seen in the amplitude of the spatial extent of flux reduction (compare figures 3 and 4). Thus we conclude that mepivacaine antagonizes the action of ornipressin mainly in the postcapillary bed. The existence of an antagonism between various local anaesthetics and vasoconstrictors, including felypressin, has been observed in several studies [17, 18].

The ratio between dilator and constrictor effects on precapillary vessels may be different in other vascular beds in which nociceptor density and vasoactivity of local anaesthetics may differ. In the extradural space of the dog, plain 2% lignocaine causes a marked depression in spinal blood flow (microsphere flowmetry [19]), whilst in man the addition of adrenaline significantly reduces the leakage of the drug into the circulation and prolongs anaesthesia [20].

The present data give further support to the view of Covino [21] that vasoconstrictive and anaesthetic potency of a local anaesthetic are unrelated.

ACKNOWLEDGEMENTS

We are grateful to E. Eidam, E. Naudascher and G. Radler who prepared the figures, and to G. McGregor for assistance with the English language. Hans Evers, Södertälje, and Hans Nolte, Minden, prompted us to study the vasoactivity of local anaesthetics.

REFERENCES

1. Blair MR. Cardiovascular pharmacology of local anaesthetics. *British Journal of Anaesthesia* 1975; **47**: 247–252.
2. Aps C, Reynolds F. The effect of concentration on vasoactivity of bupivacaine and lignocaine. *British Journal of Anaesthesia* 1976; **48**: 1171–1174.
3. Fairley JW, Reynolds F. An intradermal study of the local anaesthetic and vascular effects of the isomers of mepivacaine. *British Journal of Anaesthesia* 1981; **53**: 1211–1215.
4. Reynolds F, Bryson THL, Nicholas ADG. Intradermal study of a new local anaesthetic agent: aptocaine. *British Journal of Anaesthesia* 1976; **48**: 347–354.
5. Willatts DG, Reynolds F. Comparison of the vasoactivity of amide and ester local anaesthetics. *British Journal of Anaesthesia* 1985; **57**: 1006–1011.
6. Mesnil de Rochemont W, Hensel, H. Messung der Hautdurchblutung am Menschen bei Einwirkung verschiedener Lokalanaesthetica. *Naunyn-Schmiedeberg's Archiv für Experimentelle Pathologie und Pharmakologie* 1960; **239**: 464–474.
7. Cederholm I, Evers H, Löfström JB. Effect of intradermal injection of saline or a local anaesthetic agent on skin blood flow—a methodological study in man. *Acta Anaesthesiologica Scandinavica* 1991; **35**: 208–215.
8. Fruhstorfer H, Nolte H, Ziegenhagel U. Hautdurchblutung nach subkutaner Lidocain-Infiltration mit und ohne Zusatz von Adrenalin oder Ornipressin. *Regional-Anaesthesie* 1990; **13**: 97–100.
9. Holloway GA. Cutaneous blood flow responses to injection trauma measured by laser Doppler velocimetry. *Journal of Investigative Dermatology* 1980; **74**: 1–4.
10. Lynn B. Neurogenic inflammation. *Skin Pharmacology* 1988; **1**: 217–224.
11. Carpenter RL, Morell RC. Bupivacaine and lidocaine are more potent vasodilators than mepivacaine: effects determined by anesthetic concentrations. *Anesthesiology* 1988; **69**: A873.
12. Fruhstorfer H, Selbmann O, Ziegenhagel U. Automatic scanner for multi-point laser Doppler flux recordings on human skin. *Skin Pharmacology* 1991; **4**: 113–116.
13. Jorfeldt L, Löfström B, Pernow B, Wahren J. The effect of mepivacaine and lidocaine on forearm resistance and capacitance vessels in man. *Acta Anaesthesiologica Scandinavica* 1970; **14**: 183–201.
14. Vallance P, Collier J, Moncada S. Effects of endothelium-derived nitric oxide on peripheral arteriolar tone in man. *Lancet* 1989; **2**: 997–999.
15. Vallance P, Collier J, Moncada S. Nitric oxide synthesised from L-arginine mediates endothelium dependant dilatation

in human veins *in vivo*. *Cardiovascular Research* 1989; **23**: 1053–1057.

16. Crossman DC, Brain SD, Fuller RW. Potent vasoactive properties of endothelin 1 in human skin. *Journal of Applied Physiology* 1991; **70**: 260–266.
17. Pateromichelakis S. Effects of mepivacaine, prilocaine and lidocaine on the induced constriction of the maxillofacial vasculature of the rat. *Acta Anaesthesiologica Scandinavica* 1991; **35**: 60–64.
18. Pateromichelakis S, Rood JP. The effect of i.a. lignocaine on adrenaline-induced vasoconstriction. *British Journal of Anaesthesia* 1986; **58**: 649–652.
19. Mitchell P, Goad R, Erwin CW, Camporesi EM, Moon RE, Watkins WD, Bennet PB. Effect of epidural lidocaine on spinal cord blood flow. *Anesthesia and Analgesia* 1989; **68**: 312–317.
20. Ohno H, Watanabe M, Saitoh J, Saegusa Y, Hasegawa Y, Yonezawa T. Effect of epinephrine concentration on lidocaine disposition during epidural anesthesia. *Anesthesiology* 1988; **68**: 625–628.
21. Covino BG. Toxicity and systemic effects of local anesthetic agents. In: Strichartz GR, ed. *Local Anesthetics. Handbook of Experimental Pharmacology*, Vol. 81. Berlin, Heidelberg, New York: Springer, 1987; 187–212.

British Journal of Anaesthesia 1993; **70**: 173–180

ANAESTHESIA AFFECTS PLASMA CONCENTRATIONS OF VASOPRESSIN, VON WILLEBRAND FACTOR AND COAGULATION FACTOR VIII IN CARDIAC SURGICAL PATIENTS

A. KUITUNEN, M. HYNYNEN, M. SALMENPERÄ, V. RASI, A. JÄRVINEN, M. SCHEININ, P. J. NEUVONEN AND F. FYHRQUIST

SUMMARY

Operative stress may affect haemostatic mechanisms through hormonal systems. As the endocrine stress response to surgery may be modulated by anaesthesia, we have altered stress hormone concentrations by using either opioid or inhalation based anaesthesia to study haemostatic mechanisms in cardiac surgical patients. Thirty patients undergoing coronary artery surgery were allocated randomly to receive fentanyl (non-stress group) or enflurane (stress group) as the main anaesthetic agent. After cardiopulmonary bypass (CPB), plasma arginine vasopressin (AVP) concentrations were significantly ($P < 0.001$) greater in the stress group (81.8 (46.9–142.9) pg ml^{-1}, mean with 95% confidence limits) than in the non-stress group (5.8 (3.3–10.2) pg ml^{-1}). Plasma noradrenaline and adrenaline concentrations increased similarly in both groups after CPB. Plasma concentrations of both von Willebrand factor (stress: 1.56 (1.33–1.79) iu ml^{-1}; non-stress: 1.00 (0.76–1.25) iu ml^{-1}) and coagulation factor VIII: C (stress 1.15 (0.87–1.44) iu ml^{-1}; non-stress: 0.69 (0.55–0.80) iu ml^{-1}) were significantly ($P < 0.01$) greater in the stress group than in the non-stress group after CPB. The results indicate that there is a temporal relationship between the increased plasma concentrations of AVP and von Willebrand factor and factor VIII: C. It is not clear if this indicates a causal relationship. However, variable stress control by anaesthesia may modify haemostasis in cardiac surgical patients. (Br. J. Anaesth. 1993; **70**: 173–180)

KEY WORDS

Blood: coagulation. Hormones: vasopressin. Surgery: cardiopulmonary bypass.

The endocrine response to surgery is characterized by increased plasma concentrations of stress-related hormones [1]. This response is especially pronounced during cardiopulmonary bypass (CPB) in patients undergoing cardiac surgery [2, 3]. Anaesthesia with large doses of opioids attenuates but does not abolish the stress response to cardiac surgery [4–6], while inhalation anaesthesia in small to moderate inspiratory concentrations is less effective [7–9].

Surgical stress activates the fibrinolytic system and increases plasma concentrations of coagulation factors with an increase in plasma arginine vasopressin (AVP) concentration [10, 11]. This suggests a possible causal relationship between stress hormones and regulation of haemostasis. Administration of exogenous adrenaline or vasopressin in large physiological concentrations induces increases in plasma concentrations of von Willebrand factor (vWF) and factor VIII: C and activates the fibrinolytic system in healthy volunteers [12–15].

Because various hormones seem to be involved in haemostatic regulation, we posed the hypothesis that the endocrine response to cardiac surgery might affect haemostasis. Therefore, we measured plasma concentrations of AVP, catecholamines and coagulation factor in patients undergoing coronary artery bypass grafting (CABG). Anaesthesia was designed to blunt the endocrine response to surgery in one group of patients, while a second group (stress group) was anaesthetized with a combination of anaesthetics thought not to abolish effectively the hormonal changes.

PATIENTS AND METHODS

The study was approved by the Hospital Ethics Committee. Patients with a history of previous cardiac surgery or coagulation disorder or those who had received coumarin anticoagulants, heparin or acetylsalicylic acid within 5 days before surgery were not entered in the study. Written informed consent was obtained from 34 patients undergoing elective primary CABG.

ANNE KUITUNEN, M.D.; MARKKU HYNYNEN, M.D.; MARKKU SALMENPERÄ, M.D. (Department of Anaesthesia); ANTERO JÄRVINEN, M.D. (Department of Thoracic and Cardiovascular Surgery); FREJ FYHRQUIST, M.D. (IV Department of Medicine); Helsinki University Central Hospital, Haartmaninkatu 4, SF-00290 Helsinki, Finland. VESA RASI, M.D., Finnish Red Cross Blood Transfusion Service, Helsinki, Finland. MIKA SCHEININ, M.D.; PERTTI J. NEUVONEN, M.D.; Department of Pharmacology, University of Turku, Turku, Finland. Accepted for Publication: July 17, 1992.

Correspondence to A.K.

Anaesthesia

Patients were premedicated with lorazepam 0.06 mg kg^{-1} i.m. 2 h before induction of anaesthesia. The regular oral cardiovascular medication of the patients was given with the premedication. Consecutive patients were allocated randomly to one of two groups. The operating surgeon did not know to which group the patient belonged.

In the *non-stress group*, anaesthesia was induced with fentanyl 50 µg kg^{-1}, diazepam 0.3 mg kg^{-1} and pancuronium 0.1 mg kg^{-1}. A continuous infusion of fentanyl was started immediately after induction of anaesthesia, at a rate of 0.3 µg kg^{-1} min^{-1} until the start of CPB and thereafter 0.15 µg kg^{-1} min^{-1} until the end of operation. When required, enflurane was administered to keep the systolic arterial pressure (SAP) less than 150 mm Hg during the prebypass period. Ephedrine, in 2.5–5 mg increments, was given to maintain SAP greater than 80 mm Hg. During CPB, mean arterial pressure was maintained between 30 and 80 mm Hg by giving either phenylephrine, in 100–200 µg increments, or by adding enflurane to the fresh gas flow of the oxygenator. After CPB, enflurane was administered when SAP was greater than 130 mm Hg.

In the *stress group*, anaesthesia was induced with thiopentone 2–4 mg kg^{-1}, fentanyl 5 µg kg^{-1} and pancuronium 0.1 mg kg^{-1}. Thereafter, anaesthesia was maintained with enflurane. Enflurane was administered according to the same arterial pressure limits as in the fentanyl group before and during CPB. However, enflurane was given in inspiratory concentrations of at least 0.2 vol % to all patients in the enflurane group before and during CPB. After CPB, enflurane was administered as soon as SAP exceeded 90 mm Hg, if at the same time cardiac index was greater than 2.4 litre min^{-1} m^{-2} and there were no arrhythmias.

Diazepam 0.3 mg kg^{-1} was administered during CPB to all patients in both groups. After operation, the patients were considered to be awake when they could give correct responses to two questions by moving the head or limbs. After CPB, dopamine and nitroglycerine infusions were given in both groups according to clinical criteria.

Cardiopulmonary bypass

During CPB, non-pulsatile flow and membrane oxygenation (Capiox, Terumo Corporation, Tokyo, Japan) were used. The extracorporeal circuit was primed with 2000 ml of Ringer's acetate solution. The patients were subjected to moderate systemic hypothermia (nasopharyngeal temperature 28–30 °C). The pump flow was maintained at 2.4 litre min^{-1} m^{-2} during cooling and rewarming, and at 1.6 litre min^{-1} m^{-2} during hypothermia. Topical myocardial cooling, together with intermittent cold potassium cardioplegia solution, were used for myocardial protection. PCV was maintained greater than 20% during CPB by giving packed red cells. Administration of heparin and protamine was based on the individual heparin dose-activated coagulation time–response curves.

Fluid therapy

After induction of anaesthesia, one unit of blood was withdrawn from the patient and replaced with 1000 ml of Ringer's acetate solution. This autologous blood unit was given back to the patient after the available residual oxygenator perfusate had been returned after CPB. An additional dose of protamine 25 mg was given for each 500 ml of this residual oxygenator perfusate. Postoperative PCV was maintained at approximately 30% by giving packed red cells and Ringer's acetate solution as required. Blood loss and total haemoglobin loss through the chest tubes were measured from sternal closure until the first morning after operation.

Laboratory analyses

Blood samples for laboratory analyses were collected into plastic syringes via a radial artery cannula. A slow saline infusion containing no heparin was used to maintain the patency of the cannula. Samples were taken at the following times: before operation after induction of anaesthesia; 15 min after the end of CPB; 2 h after CPB; 5.5 h after CPB; 16 h after CPB. An additional sample for measurement of plasma AVP was also obtained during CPB at maximal hypothermia. Plasma samples were frozen (−70 °C) until the assay of hormones and coagulation factors. Protamine was given before the second sample. The autologous blood unit and residual oxygenator perfusate were returned to the patient between the second and third samples.

Plasma AVP concentration was measured using a previously described radioimmunoassay method [16] with an intra-assay coefficient of variation of 8% and an inter-assay coefficient of variation of 14%. Plasma catecholamine concentrations (noradrenaline and adrenaline) were measured using high pressure liquid chromatography with coulometric electrochemical detection (HPLC-EC), as reported previously [17]. The intra-assay coefficient of variation was 2% and the inter-assay coefficient of variation was 3%.

PCV and platelet count in whole blood were determined using a Sysmex Analyzer (Toa Medical Electronics, Hamburg, Germany). Platelet adhesion was studied by measuring platelet retention on glass beads [18]. For the measurement, arterial blood was drawn through Adeplat S column at a constant flow rate using a Adeplat pump (Semmelweiss, Milano, Italy). After the first 2 ml of the effluent was discarded, platelet count in the third 1 ml was measured and subtracted from that in an aliquot of unfiltered blood. The difference in platelet counts (glass bead retention) was calculated in per cent of platelet count in the unfiltered blood and expressed as platelet adhesion. Template bleeding time determination (BT) was performed on the volar surface of the forearm with Simplate II device (General Diagnostics, Organon Teknika, Turnout, Belgium). Plasma β-thromboglobulin assay (β-TG) was performed using a method described previously [19].

Serum total protein concentration, plasma fibrinogen, activated partial thromboplastin time (APTT) and prothrombin time (PT) were determined using standard techniques. von Willebrand factor antigen (vWF) was assayed by immunoelectrophoresis [20]. Factor VIII procoagulant activity (factor VIII:C) was assayed with a one-stage kaolin–cephalin time method utilizing factor VIII:C-deficient plasma as a substrate [21]. The factor VIII:C-deficient plasma was obtained from a patient with severe haemophilia A (factor VIII:C < 0.01 iu ml^{-1}). Factor V was assayed by one-stage prothrombin time technique [22]. The reference plasma for the determination of these coagulation factors was citrated plasma pooled from 20 healthy blood donors in Finnish Red Cross Blood Transfusion Service. Thromboelastograph (TEG) tracings (Hellige Company, Freiburg, Germany) were obtained from citrated whole blood. Coagulation was initiated by adding calcium chloride to the cuvettes. TEG tracings were analysed by measuring reaction time (R), coagulation time (R+K), clot formation (α-angle) and maximum amplitude [23].

Statistical analyses

Analysis of variance (ANOVA) for repeated measurements was first applied for statistical comparisons within and between the groups. For statistical significance after ANOVA, the means were compared between and within the groups with Sheffé's F test. Within groups, the values were compared with the value obtained after the induction of anaesthesia. The values between the groups were compared at each sample time. Log-transformation was applied to hormone data before statistical analyses because of skewed data. Two-tailed Fisher's exact test was applied to compare data of quantal nature. The number of internal mammary artery grafts (one or two) was used as a covariate in the analysis of covariance for comparisons of blood loss and total haemoglobin loss between the groups. $P < 0.05$ was considered statistically significant. Results are given as the arithmetic mean with SEM or 95% confidence limits, with the exception of the hormone results, which are presented as the geometric mean with 95% confidence limits.

RESULTS

Four of the 34 patients were excluded from the study. One of these had been allocated to the non-stress group. She had cardiac failure after operation and died soon after the operation. Three excluded patients had been allocated to the stress group. One had cardiac failure after operation and had to be treated with adrenaline. Two excluded patients required re-operation because of postoperative bleeding; the bleeding site was identified clearly in both. The haemostatic variables of these excluded patients did not differ from those of the remaining patients.

The final study groups were comparable in preoperative characteristics (table I). There was a slightly greater proportion of male patients in the non-stress group; mean weight was slightly larger in the stress group. However, there was no significant difference between the groups in weight or body mass index (wt ht^{-2}). In spite of the randomization, the number of patients with two internal mammary artery grafts was not similar in the groups (10 patients in the non-stress group *vs* three patients in the stress group; $P = 0.025$). All other intraoperative variables were comparable (table I). The preoperative values of the coagulation variables were also similar in the groups (table II). Awakening occurred significantly earlier in the stress group than in the non-stress group (87 (14) min *vs* 321 (102) min after the end of surgery; $P < 0.001$).

TABLE I. *Patient and surgical data (mean (range or* SEM*) or number of patients). LV = left ventricle; CPB = cardiopulmonary bypass; IMA = internal mammary artery.* **P < 0.01 *between groups*

	Non-stress group	Stress group
Sex (M/F)	14/1	9/6
Age (yr)	59 (50–70)	56 (39–63)
Weight (kg)	78 (3)	80 (5)
Height (cm)	172 (2)	168 (3)
Blood group O	5	5
Preoperative medication		
Beta-blocker	12	12
Calcium channel blocker	7	11
Nitrates	12	12
LV ejection fraction (%)	63 (5)	62 (3)
CPB time (min)	103 (6)	96 (8)
Operation time (min)	244 (10)	227 (16)
Aortic cross-clamp time (min)	51 (3)	46 (5)
Number of distal coronary anastomoses	4 (0)	3 (0)
Number of patients with two IMA grafts	10	3 **
Number of chest tubes	3 (0)	3 (0)

Plasma concentration of AVP did not differ between the groups immediately after induction of anaesthesia (fig. 1), but the AVP concentration was greater during CPB in the stress group than in the non-stress group (92.0 (50.7–133.2) pg ml^{-1} *vs* 8.5 (5.1–11.9) pg ml^{-1}; $P < 0.001$) (data not shown in fig. 1). There was a significant difference between the groups immediately after CPB, because plasma AVP concentration increased 20-fold from the value after induction in the stress group (fig. 1). The plasma concentration of AVP was significantly greater in the stress group than in the non-stress group at 2 h after CPB also. Until 5.5 h after CPB, plasma AVP concentration had increased also in the non-stress group, and there was no significant difference between the groups. On the first morning after operation, plasma AVP concentration had returned to the value after induction in both groups. Although there was a slightly greater proportion of females in the stress group, there was no difference in the AVP values between the sexes in the stress group.

Plasma concentrations of adrenaline and noradrenaline increased significantly in both groups immediately after CPB and remained increased until the end of the study. There was no significant difference between the groups at any stage (fig. 1).

PCV, serum total protein and platelet count decreased significantly after CPB in both groups (table II). There were no significant differences between the groups in PCV and serum concentration of total protein at any stages of the study, but platelet count was greater in the stress group 2 h and 5.5 h after CPB and on the first morning after operation. The decrease in platelet adhesion was significant in the non-stress group immediately after CPB, but this decrease was not significantly different from that observed in the stress group. Platelet adhesion recovered within 2 h after CPB and remained recovered for the rest of the study in both groups (table II). Plasma concentration of β-thromboglobulin increased significantly immediately after CPB in both groups, but had returned to the post-induction value until the first morning after operation. The bleeding time was significantly prolonged 2 h and 5.5 h after CPB in both groups. There was no significant difference between the groups in plasma concentration β-thromboglobulin or bleeding time at any stage of the study (table II).

Plasma concentration of factor VIII:C did not change significantly in the two groups immediately after CPB (fig. 2) but, because of a slight increase in the stress group and a slight decrease in the non-stress group, a significant difference in factor VIII:C concentration occurred between groups immediately after CPB. During the later course of the study, plasma concentration of factor VIII:C increased in both groups. Factor VIII:C concentration was increased significantly more in the stress group 2 h after CPB. However, 5.5 h after CPB and on the first morning after operation there was no difference between the groups. A similar course of changes was observed in von Willebrand factor. On the first morning after operation vWF concentration increased nearly two-fold in both groups compared with the postinduction values (fig. 2).

In both groups, plasma fibrinogen concentration decreased significantly after CPB, but returned to

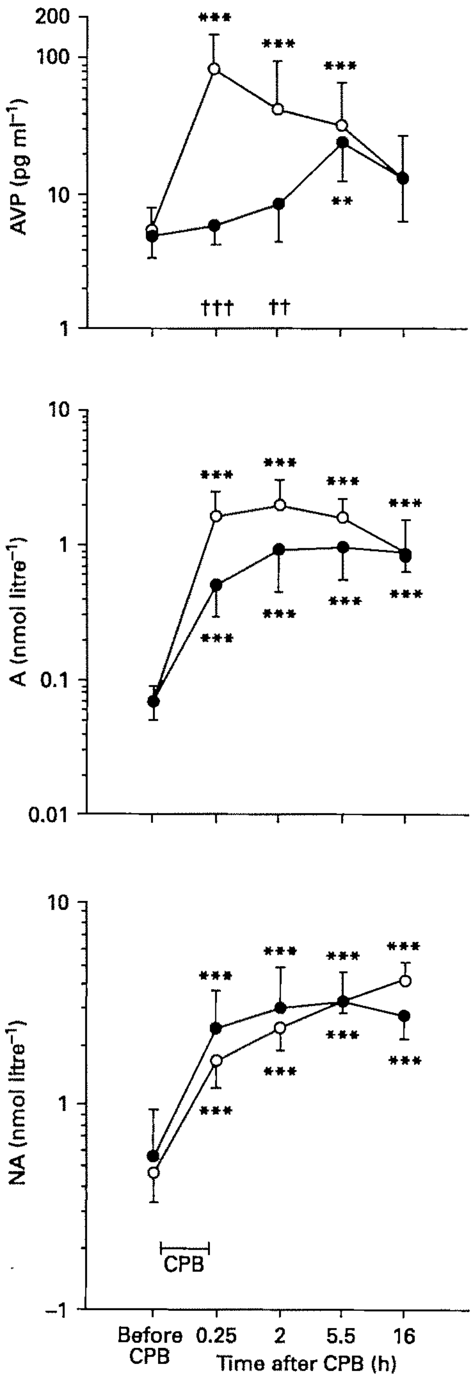


FIG. 1. Plasma concentrations (mean, 95% confidence limits) of arginine vasopressin (AVP), noradrenaline (NA) and adrenaline (A). ○ = Stress; ● = non-stress **$P < 0.01$, ***$P < 0.001$ compared with preoperative (postinduction) value within a group. ††$P < 0.01$, †††$P < 0.001$ between the groups compared.

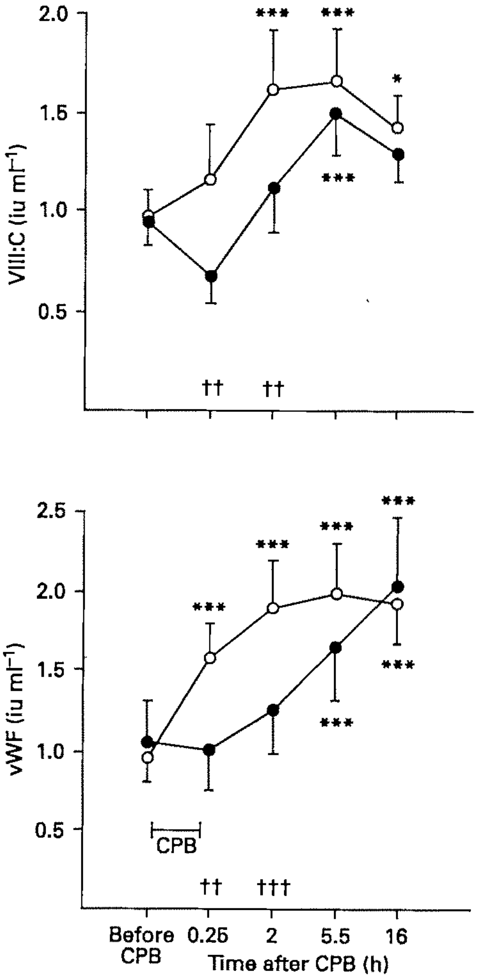


FIG. 2. Plasma concentrations (mean, 95% confidence limits) of factor VIII procoagulant activity (VIII:C) and von Willebrand factor (vWF). ○ = Stress; ● = non-stress. *$P < 0.05$, ***$P < 0.001$ compared with preoperative (postinduction) value within a group. ††$P < 0.01$, †††$P < 0.001$ between the groups compared.

TABLE II. Data on haemodilution, platelets and coagulation times (mean (95% confidence limits)). No = Non-stress group; yes = stress group; PCV = packed cell volume; Protein = serum total protein; Fbg = plasma fibrinogen; PC = platelet count; Adhesion = platelet adhesion; β-TG = β-thromboglobulin; BT = bleeding time; APTT = activated partial thromboplastin time; PT = prothrombin time; TEG:R = TEG reaction time; TEG:R+K = TEG R+K time; TEG:α = α-angle; TEG:MA = maximal amplitude from thromboelastograph tracing. — = Values not available. *P < 0.05, **P < 0.01, ***P < 0.001 compared with preoperative (postinduction) value within a group; †P < 0.05, ††P < 0.01 between groups

		After CPB			
	Before CPB	0.25 h	2 h	5.5 h	16 h
PCV (%)					
No	37 (35–39)	27*** (26–28)	32** (30–34)	31** (29–33)	31** (29–33)
Yes	37 (35–39)	28*** (26–30)	33** (31–35)	32** (30–34)	31** (30–32)
Protein (g litre^{-1})					
No	61.0 (59.2–62.8)	38.1*** (36.7–39.5)	45.7*** (43.5–47.9)	44.9*** (42.3–47.5)	49.9*** (46.7–53.1)
Yes	59.4 (56.9–61.9)	38.9*** (36.3–41.5)	49.2*** (46.0–52.4)	48.6*** (45.6–51.6)	49.9*** (47.4–52.4)
Fbg (g litre^{-1})					
No	2.6 (2.4–2.8)	1.6*** (1.4–1.8)	1.9*** (1.7–2.1)	2.0*** (1.8–2.2)	2.7 (2.5–2.9)
Yes	2.9 (2.6–3.2)	1.9*** (1.7–2.1)	2.3*** (2.1–2.5)	2.5** (2.3–2.7)	3.2 (2.9–3.5)
PC ($\times 10^9$ litre^{-1})					
No	172 (156–188)	114*** (99–129)	125*** (111–139)	130** (113–147)	116*** (101–131)
Yes	192 (167–217)	133*** (113–153)	159**†† (137–181)	161*† (136–186)	146**† (127–165)
Adhesion (%)					
No	76 (62–90)	37*** (20–54)	79 (63–95)	86 (79–93)	83 (66–100)
Yes	70 (50–90)	50 (29–71)	84 (73–95)	73 (55–91)	76 (58–94)
β-TC (ng litre^{-1})					
No	36.7 (24.9–48.5)	151.7*** (119.4–184.1)	—	—	62.3 (41.7–82.9)
Yes	31.5 (22.1–40.9)	191.7*** (142.5–240.9)	—	—	45.8 (36.9–54.7)
BT (min)					
No	6.4 (5.7–7.4)	—	10.2*** (8.1–12.3)	8.5** (6.8–10.2)	—
Yes	6.0 (5.2–6.8)	—	8.0** (6.5–9.5)	7.6* (6.4–8.8)	—
Factor V (iu ml^{-1})					
No	0.87 (0.74–1.00)	0.51*** (0.40–0.62)	0.72* (0.61–0.83)	0.71* (0.59–0.83)	0.73 (0.65–0.81)
Yes	0.87 (0.77–0.97)	0.57*** (0.48–0.66)	0.74 (0.65–0.83)	0.82 (0.76–0.90)	0.91† (0.83–0.99)
APTT (s)					
No	31 (30–32)	41*** (39–43)	32 (30–34)	33 (29–37)	34 (31–37)
Yes	29 (27–31)	40*** (34–46)	29 (27–31)	30 (28–32)	32 (30–34)
PT (%)					
No	96 (88–104)	63*** (55–71)	77** (72–82)	75*** (68–82)	64*** (54–74)
Yes	100 (88–112)	62*** (53–71)	79*** (70–88)	81*** (74–88)	73*** (65–81)
TEG:R (min)					
No	6.6 (5.8–7.4)	5.6 (5.1–6.1)	5.3 (4.3–6.3)	5.0 (4.1–5.9)	4.6* (3.9–5.3)
Yes	6.6 (5.9–7.3)	6.7 (4.8–8.6)	5.2 (4.7–5.7)	5.3 (4.6–6.0)	4.9 (4.1–5.7)
TEG:R+K (min)					
No	12.5 (11.2–13.8)	12.4 (10.8–14.0)	11.4 (10.0–12.8)	11.6 (8.7–14.5)	9.3* (8.4–10.2)
Yes	12.0 (10.2–13.8)	12.6 (10.4–14.8)	10.5 (9.2–11.8)	11.7 (9.1–14.3)	8.6* (7.8–9.4)
TEG:α (deg.)					
No	41 (38–44)	38 (35–41)	40 (36–44)	41 (36–46)	48 (44–52)
Yes	44 (39–49)	37** (30–44)	43 (38–48)	45 (39–51)	54* (50–58)
TEG:MA (mm)					
No	45 (43–47)	42 (38–46)	42 (39–45)	42 (38–46)	48 (45–51)
Yes	50 (46–54)	42*** (36–48)	44** (41–47)	45 (41–49)	49 (45–53)

TABLE III. *Cumulative blood loss and total haemoglobin loss during the postoperative period (mean (SEM))*

	Non-stress group	Stress group
Blood loss (ml)	1034 (83)	828 (41)
Haemoglobin loss (g)	55 (7)	37 (3)

the preoperative value until the first morning after operation (table II). Factor V concentration declined significantly immediately after CPB in both groups, but returned to control values thereafter. However, on the first morning after operation, factor V concentration was significantly greater in the stress group. APTT values were slightly but significantly prolonged 15 min after CPB in both groups, but thereafter APTT values did not differ from the values after induction. PT values decreased from baseline during the whole study period. There was no significant difference between the groups in either APTT or PT. There were also no significant differences in any TEG parameter between the groups. TEG reaction time was significantly decreased from the value after induction on the first morning after operation in the non-stress group. TEG R+K time decreased significantly from postinduction values on the first morning after operation in both groups. Compared with the value after induction, TEG α-angle decreased significantly 15 min after CPB and increased significantly on the morning after operation in the stress group. The maximal amplitude of the TEG tracing decreased significantly 0.25 h and 2 h after CPB in the stress group.

Postoperative blood loss and total haemoglobin loss were significantly smaller ($P = 0.0342$ and 0.0224, respectively) in the stress group than in the non-stress group. After the number of internal mammary artery grafts was used as a covariate in the analysis of covariance, there were no statistically significant differences in blood loss and total haemoglobin loss between the groups ($P = 0.162$ and 0.222, respectively).

DISCUSSION

The present study confirmed our earlier finding that fentanyl, administered continuously in a large dose and supplemented with other anaesthetics, abolished the vasopressin response to cardiac surgery for as long as the opioid was infused [6]. However, this anaesthetic method is not totally "stress free", because similar catecholamine responses were noticed in both groups immediately after CPB. In contrast, and as expected, the enflurane-based anaesthetic method did not prevent the endocrine response to surgery. The increase in plasma concentration of AVP in the enflurane-anaesthetized patients (stress group) after CPB and thereafter and in the fentanyl-anaesthetized patients (non-stress group) after operation was associated temporally with an increase in plasma concentrations of von Willebrand factor and factor VIII. A similar relationship was not observed with plasma concentrations of catecholamines and the coagulation factors. These findings suggest that the stress-related increase in plasma concentration of AVP, or some other stress factors not identified in this study (but not catecholamines), may affect haemostasis in cardiac surgical patients after bypass.

Marked increases in plasma concentrations of numerous stress-related hormones, such as cortisol, AVP, noradrenaline and adrenaline, have been reported in association with cardiac surgery. Cardiopulmonary bypass seems to be a potent trigger to increase the concentrations of these hormones [2, 3]. The hormonal responses to CPB have been attenuated with the administrations of both i.v. [6] and volatile [24] anaesthetics. In our stress group, the anaesthetic (enflurane) concentration was adjusted according to the arterial pressure response, whilst the opioid was given in a fixed dose. Thus the level of anaesthesia might occasionally have been lighter in the volatile anaesthetic group. Therefore, our results do not allow us to grade one anaesthetic technique as superior to the other as far as suppression of the endocrine response to cardiac surgery is concerned.

We found that our fentanyl technique attenuated the vasopressin response to CPB, but did not abolish the catecholamine response. The inhibitory effect of fentanyl on the stress response seems to be mediated (directly or indirectly) via the hypothalamus [25]. This effect of fentanyl decreases the AVP release. The lack of effect of high-dose fentanyl on the sympathoadrenal response to CPB is in agreement with the observations of others [26, 27].

AVP acts as an antidiuretic hormone at plasma concentrations of a few pg ml^{-1}. However, under certain conditions such as surgery, considerably greater plasma AVP concentrations may prevail [10, 11, 28, 29]. These very large concentrations, known to induce vasocontriction, are associated with increases in plasma concentrations of factor VIII and vWF [10, 11]. Such a relationship existed also in our patients. Observations in studies using infusion of exogenous AVP to man suggest that there is a threshold plasma AVP concentration of 20–25 pg ml^{-1} at which an increase in plasma concentration of factor VIII occurs [14, 15]. Our results agree with this suggestion, as a significant difference in plasma concentrations of vWF and factor VIII:C between the groups existed after CPB until the mean plasma concentration of AVP had increased to more than 20 pg ml^{-1}. Our observations support the hypothesis that AVP has a physiological role in the acute regulation of haemostasis in surgical patients [30]. Increased catecholamine release does not seem to play a determinant role in the acute regulation of haemostasis. During colonoscopy, plasma concentrations of factor VIII:C and vWF increased with an increase in plasma concentration of AVP, while plasma catecholamine concentrations remained unchanged [29]. In our study, there was no difference in catecholamine concentrations between the groups.

Large molecular weight multimers of vWF act as a glue to overcome high shear forces between circulating platelets and collagen exposed by endothelial injury. Loss of glycoprotein Ib receptors which bind vWF to platelet surfaces may be an important part of acquired platelet dysfunction induced by CPB [31]. Clinical studies suggest that increases in concentrations of the adhesive agonist, vWF, to greater than those known to be critical for adequate haemostasis in non-cardiac surgery, may improve haemostasis after CPB [32, 33]. Although plasma concentrations of vWF did not decline to less than prebypass values, there was a difference in the plasma vWF concentration between the two groups and this may have a potential to cause a difference in haemostasis.

We did not observe significant differences between the groups in clotting times and coagulation factors other than factor VIII:C and vWF. However, we observed a greater platelet count in the stress group from 2 h after CPB until the first morning after operation. This finding is consistent with a previous report that stress (exercise-induced) produced a transient thrombocytosis via an effect on the spleen [34]. However, when we compared changes from the baseline values of platelet count between our two groups, there was no difference.

The blood loss and total haemoglobin loss measured after operation were significantly smaller in the stress group. However, the significant difference in the number of internal mammary artery grafts between groups may have affected this. It has been shown that the use of bilateral internal mammary artery grafts in CABG increases requirements for blood transfusion compared with one graft only [35]. To assess this, we used the number of these grafts as a covariate in the analysis of the data. With this procedure, there was no statistically significant difference in blood loss and haemoglobin loss between the groups. In order to reach statistical significance for the observed difference in blood loss or total haemoglobin loss between the groups, the sample size should have been about 100 patients with a statistical power of 0.80 and a significance level of 0.05. Thus the implications of the effects of anaesthesia on plasma AVP and coagulation factor concentrations on clinical haemostasis will require investigation in a much larger study.

The choice of the anaesthetic technique in patients undergoing CABG does not seem to affect postoperative cardiac complications and overall outcome [36, 37]. However, the method used to control surgical stress may contribute to the acquired haemostatic defect after CPB, by affecting the plasma concentrations of haemostatic factors.

ACKNOWLEDGEMENTS

We thank Jussi Heinonen, M.D. and Gunnar Myllylä, M.D. for their critical review of the manuscript. We thank Elina Vahtera, PHIL.LIC., Ms Päivi Aho, Mrs Mailis Himberg and the personnel in the Laboratory of Haemostasis at the Finnish Red Cross Transfusion Service for their assistance. The study was supported by grants from the Paulo Foundation, the Instrumentarium Foundation and Helsinki University Central Hospital.

REFERENCES

1. Hall GM. The anaesthetic modification of the endocrine and metabolic response to surgery. *Annals of the Royal College of Surgeons of England* 1985; **67**: 25–29.
2. Reves JG, Croughwell N, Jacobs JR, Greeley W. Anesthesia during cardiopulmonary bypass: does it matter? In: Tinker HJ, ed. *Cardiopulmonary Bypass: Current Concepts and Controversies*. Philadelphia: W. B. Saunders, 1989; 69–97.
3. Bovill JG, Sebel PS, Stanley TH. Opioid analgesics in anesthesia: with special reference to their use in cardiovascular anesthesia. *Anesthesiology* 1984; **61**: 731–755.
4. Lacoumenta S, Yeo TH, Paterson JL, Burrin JM, Hall GM. Hormonal and metabolic responses to cardiac surgery with sufentanil–oxygen anaesthesia. *Acta Anaesthesiologica Scandinavica* 1987; **31**: 258–263.
5. de Lange S, Boscoe MJ, Stanley TH, de Bruijin N, Philbin DM, Coggins CH. Antidiuretic and growth hormone responses during coronary artery surgery with sufentanil–oxygen and alfentanil–oxygen anesthesia in man. *Anesthesia and Analgesia* 1982; **61**: 434–438.
6. Hynynen M, Lehtinen A-M, Salmenperä M, Fyhrquist F, Takkunen O, Heinonen J. Continuous infusion of fentanyl or alfentanil for coronary artery surgery. Effects on plasma cortisol concentration, β-endorphine immunoreactivity and arginine vasopressin. *British Journal of Anaesthesia* 1986; **58**: 1260–1266.
7. Philbin DM, Coggins CH. Plasma antidiuretic hormone levels in cardiac surgical patients during morphine and halothane anesthesia. *Anesthesiology* 1978; **49**: 95–98.
8. Kono K, Philbin DM, Coggins CH, Moss J, Rosow CE, Schneider RC, Slater EE. Renal function and stress response during halothane or fentanyl anesthesia. *Anesthesia and Analgesia* 1981; **60**: 552–556.
9. Zurick AM, Urzua J, Yared J-P, Estafanous FG. Comaparison of hemodynamic and hormonal effects of large single-dose fentanyl anesthesia and halothane/nitrous oxide anesthesia for coronary artery surgery. *Anesthesia and Analgesia* 1982; **61**: 521–526.
10. Grant PJ, Tate GM, Williams NS, Prentice CRM. Intraoperative activation of coagulation—a stimulus to thrombosis mediated by vasopressin? *Thrombosis and Haemostasis* 1986; **55**: 104–107.
11. Wilson J, Grant PJ, Davies JA, Boothby M, Gaffney PJ, Prentice CRM. The relationship between plasma vasopressin and changes in coagulation and fibrinolysis during hip surgery. *Thrombosis Research* 1988; **51**: 439–445.
12. Cash JD, Gader AMA, de Costa J. The release of plasminogen activator and factor VIII to lysine vasopressin, arginine vasopressin, 1-desamino-8-D-arginine vasopressin, angiotensin and oxytocin in man. *British Journal of Haematology* 1974; **27**: 363–364.
13. Mannucci PM, Åberg M, Nilsson IM, Robertson B. Mechanism of plasminogen activator and factor VIII increase after vasoactive drugs. *British Journal of Haematology* 1975; **30**: 81–93.
14. Grant PJ, Davies JA, Tate GM, Boothby M, Prentice CRM. Effects of physiological concentrations of vasopressin on haemostatic function in man. *Clinical Science* 1985; **69**: 471–476.
15. Nussey SS, Bevan DH, Ang VTY, Jenkins JS. Effects of arginine vasopressin (AVP) infusions on circulating concentrations of platelet AVP, factor VIII:C and von Willebrand factor. *Thrombosis and Haemostasis* 1986; **55**: 34–36.
16. Fyrhquist F, Wallenius M, Hollemans HJG. Radioimmunoassay of vasopressin in unextracted plasma. *Scandinavian Journal of Clinical and Laboratory Investigation* 1976; **36**: 841–847.
17. Scheinin M, Koulu M, Laurikainen E, Allonen H. Hypokalaemia and other non-bronchial effects of inhaled fenoterol and salbutamol: a placebo-controlled dose–response study in healthy volunteers. *British Journal of Clinical Pharmacology* 1987; **24**: 645–653.
18. Langley PG, Hughes RD, Williams R. Platelet adhesiveness to glass beads in liver disease. *Acta Haematology* 1982; **67**: 124–127.
19. Kuronen B, Kauppinen H-L, Rasi V, Kekomäki R, Myllylä G. A coated-tube radioimmunoassay for β-thromboglobulin. *Medical Biology* 1980; **58**: 264–268.
20. Laurell CB. Quantitative estimation of proteins by electrophoresis in agarose gel containing antibodies. *Analytical Biochemistry* 1966; **15**: 45–52.
21. Hardisty RM, MacPherson JC. A one-stage factor VIII (antihaemophilia globulin) assay and its use on venous and capillary plasma. *Thrombosis et Diathesis Haemorrhagica* 1962; **7**: 215–229.

22. Biggs R. Human blood coagulation. In: *Haemostasis and Thrombosis*. Oxford: Blackwell Scientific, 1976; 657–750.
23. Spiess BD, Ivankovich AD. Thromboelastography: a coagulation monitoring technique applied to cardiopulmonary bypass. In: Ellison N, Jobes DR, eds. *Effective Hemostasis in Cardiac Surgery*. Philadelphia: WB Saunders, 1988; 163–181.
24. Flezzani P, Croughwell ND, McIntyre RW, Reves JG. Isoflurane decreases the cortisol response to cardiopulmonary bypass. *Anesthesia and Analgesia* 1986; **65**: 1117–1122.
25. Hall GM, Lacoumenta S, Hart GR, Burrin JM. Site of action of fentanyl in inhibiting the pituitary–adrenal response to surgery in man. *British Journal of Anaesthesia* 1990; **65**: 251–253.
26. de Lange S, Stanley TH, Boscoe MJ, de Bruijin N, Berman L, Green O, Robertson D. Catecholamine and cortisol responses to sufentanil–O_2 and alfentanil–O_2 anaesthesia during coronary artery surgery. *Canadian Anaesthetists Society Journal* 1983; **30**: 248–254.
27. Samuelson PN, Reves JG, Kirklin JK, Bradley E jr, Wilson KD, Adams M. Comparison of sufentanil and enflurane–nitrous oxide anesthesia for myocardial revascularization. *Anesthesia and Analgesia* 1986; **65**: 217–226.
28. Cochrane JSP, Forsling ML, Menzies Gow N, Le Quesne LP. Arginine vasopressin release following surgical operations. *British Journal of Surgery* 1981; **68**: 209–213.
29. Hampton KK, Grant PJ, Primrose J, Dean HG, Davies JA, Prentice CRM. Haemostatic responses and vasopressin release during colonoscopy in man. *Clinical Science* 1991; **81**: 257–260.
30. Grant PJ, Medcalf RL. Hormonal regulation of haemostasis and the molecular biology of the fibrinolytic system. *Clinical Science* 1990; **78**: 3–11.
31. Van Qeveren W, Harder MP, Roozendaal KJ, Eijsman L, Wildevuur CRH. Aprotinin protects platelets against the initial effect of cardiopulmonary bypass. *Journal of Thoracic and Cardiovascular Surgery* 1990; **99**: 788–797.
32. Bagge L, Lilienberg G, Nyström S-O, Tyden H. Coagulation, fibrinolysis and bleeding after open-heart surgery. *Scandinavian Journal of Thoracic and Cardiovascular Surgery* 1986; **20**: 151–160.
33. Weinsten M, Ware JA, Troll J, Salzman E. Changes in von Willebrand factor during cardiac surgery: effect of desmopressin acetate. *Blood* 1988; **71**: 1648–1655.
34. Sarajas HSS. Reaction patterns of blood platelets in exercise. Characteristics, origin and possible coronary implications. *Advances in Cardiology* 1976; **18**: 176–195.
35. Aarnio P, Kettunen S, Harjula A. Pleural and pulmonary complications after bilateral internal mammary artery grafting. *Scandinavian Journal of Thoracic and Cardiovascular Surgery* 1991; **25**: 175–178.
36. Slogoff S, Keats AS. Randomized trial of primary anesthetic agents on outcome of coronary artery bypass operations. *Anesthesiology* 1989; **70**: 179–188.
37. Tuman KJ, McCarthy RJ, Spiess BD, DaValle M, Dabir R, Ivankovich AD. Does choice of anesthetic agent significantly affect outcome after coronary artery surgery? *Anesthesiology* 1989; **70**: 189–198.

British Journal of Anaesthesia 1993; 70: 181–185

EFFECTS OF MIDAZOLAM AND FLUNITRAZEPAM ON THE RELEASE OF DOPAMINE FROM RAT STRIATUM MEASURED BY *IN VIVO* MICRODIALYSIS

K. TAKADA, T. MURAI, T. KANAYAMA AND N. KOSHIKAWA

SUMMARY

We have studied the effects of midazolam and flunitrazepam on extracellular concentrations of dopamine, 3,4-dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA) in rat striatum in freely moving animals using in vivo *microdialysis. I.v. injections of midazolam 0.075 and 0.15 mg kg^{-1} decreased striatal dopamine concentrations in a dose-dependent manner without affecting the concentrations of DOPAC and HVA. Flunitrazepam 0.015 and 0.03 mg kg^{-1} also decreased striatal dopamine concentrations in a dose-related manner, but the reductions in DOPAC and HVA were not significant. Flumazenil 6 µg kg^{-1} alone did not affect striatal concentrations of dopamine, DOPAC and HVA, but it prevented the effects of midazolam and flunitrazepam. Flunitrazepam 10 µmol litre^{-1} also decreased striatal dopamine release when infused through a dialysis probe placed into the striatum, but it failed to affect striatal dopamine release when infused into the ipsilateral substantia nigra. Central administrations of midazolam were effective only when the drug was infused into both sites simultaneously (10 and 100 µmol litre^{-1}) or given by intraventricular injection (0.5 and 1 µg). These results suggest that midazolam and flunitrazepam affect striatal dopamine release in a different manner.* (Br. J. Anaesth. 1993; **70**: 181–185)

KEY WORDS

Brain: striatal catecholamines. Hypnotics, benzodiazepines: flunitrazepam, midazolam. Sympathetic nervous system: dopamine.

Behavioural and biochemical studies suggest that there is a functional interaction between γ-aminobutyric acid (GABA)-ergic and dopaminergic neuronal systems, especially at dopaminergic nerve terminals [1–5]. For example, GABA receptor agonists injected into the substantia nigra have been reported to reduce striatal dopamine release [6, 7]. With the brain microdialysis technique, which permits measurement of dopamine and its metabolites in discrete brain regions *in vivo*, it has also been shown that dopamine release in the striatum and nucleus accumbens is decreased by benzodiazepines administered systemically or by local intracerebral injection [8–10]. The actions of the benzodiazepines are caused by enhancement of the action of GABA and are mediated by specific binding sites which are part of the multimolecular GABA$_A$–receptor complex [10–13].

Benzodiazepines are given i.v. to produce either sedation or, when combined with an opioid analgesic, anaesthesia. Midazolam is the drug of choice for these purposes because it does not produce local venous irritation and thrombosis. However, there is still no clear understanding of its mode of action in the central nervous system.

The present study describes the effects of midazolam and of flunitrazepam, in doses similar to those used clinically, on nigrostriatal dopaminergic neuronal activity by using *in vivo* brain microdialysis to measure striatal dopamine release. As the striatum is known to be a terminal area of the dopaminergic neurones that arise from the substantia nigra [14], the compounds were also applied focally to the substantia nigra and the striatum to determine if there were differences between the sites of action of the two drugs.

MATERIALS AND METHODS

Male Sprague–Dawley rats (250–300 g body weight) were studied. Between experiments they were housed in a temperature-controlled environment on a 12-h light–dark cycle (light period 07:00–19:00) with free access to food and water.

Surgery

The rats were anaesthetized with pentobarbitone 50 mg kg^{-1} i.p. The left external jugular vein was cannulated and connected to an osmotic minipump which was filled with heparin–saline 1000 u ml^{-1} and implanted s.c. between the scapulae. The anaesthetized animals were placed in a stereotactic apparatus and unilateral guide cannulae were implanted just above the striatum (antero–posterior (AP) 9.2 mm, medio–lateral (ML) 3.0 mm, dorso–ventral (DV) 7.0 mm) and substantia nigra (AP 3.7 mm, ML 2.0 mm, DV 4.0 mm) according to

---

KOJI TAKADA, B.D.S., PH.D., TAMEATSU MURAI, B.D.S., TOSHIYOSHI KANAYAMA, M.D., PH.D. (Department of Dental Anaesthesiology); NORIAKI KOSHIKAWA, B.D.S., PH.D. (Department of Pharmacology); Nihon University School of Dentistry, 1-8-13 Kanda-Surugadai, Chiyoda-Ku, Tokyo 101, Japan. Accepted for Publication: August 4, 1992.

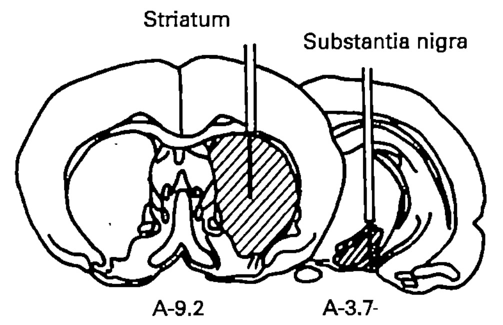


FIG. 1. Schematic illustration showing the location of the probe in the striatum and substantia nigra. Planes are taken from the atlas of Paxinos and Watson [15]; co-ordinates are in mm anterior to the interaural line.

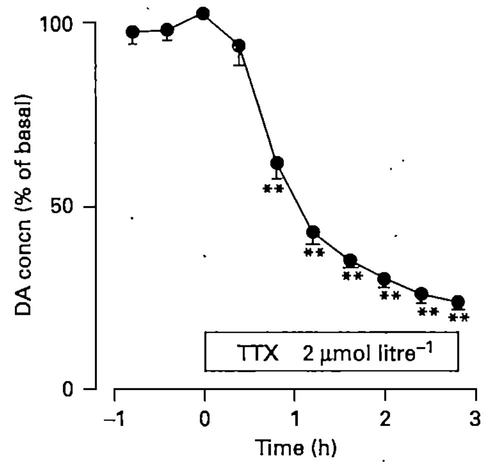


FIG. 2. Effects of infusion of tetrodotoxin (TTX) 2 μmol litre^{-1} on the concentrations of dopamine (DA) in striatal dialysates (mean, SEM of data from six rats). $^{**}P < 0.01$ compared with value just before TTX infusion (paired t test).

the atlas of Paxinos and Watson [15] (fig. 1). The guide cannulae were kept patent between experiments by stainless steel inserts. Before an experiment, the insert was removed and a dialysis probe (3 mm length for the striatum and 2 mm for the substantia nigra, 0.25 mm o.d., 50000 mol. wt "cut-off") was inserted into the guide cannulae so that only the dialysis tubing protruded from the tip. In some animals, a unilateral cannula (0.6 mm o.d., i.d. 0.3 mm) was implanted into the contralateral lateral ventricle (AP 8.2 mm, ML 1.5 mm, DV 7.0 mm) for intraventricular drug injections. The rats were then allowed to recover for a minimum of 7 days before experiments were carried out.

Dialysis and neurochemical measurements

On the day of the experiment, the probes were inserted carefully into the conscious rat and fixed to the guide cannulae by either a screw or dental cement. The rat was then placed in a plexiglass box (30 × 30 cm) and the inlet and outlet tubes connected to a swivel located on a counterbalanced beam to minimize discomfort to the rat. The probes were perfused at a rate of 2.0 μl min^{-1} with Ringer solution (composition (mmol litre^{-1}); NaCl 147, KCl 4, $CaCl_2$ 1.2, $MgCl_2$ 1.1; pH 6.0) and the outflow was connected by Teflon tubing to an HPLC system (EICOM, Kyoto, Japan). Perfusate samples were taken every 25 min for measurement of dopamine, DOPAC and HVA. When the baseline concentration of dopamine had stabilized (at least 4 h after probe insertion), drugs were injected via a jugular cannula. Baseline values were the mean of the last three samples before the injection of drug or infusion of tetrodotoxin. The probes had an *in vitro* recovery of 10–12 % for dopamine, DOPAC and HVA, but the reported concentrations were not adjusted for recovery because this cannot be estimated accurately [16, 17].

Dopamine, DOPAC and HVA were separated on an Eicompak MA-5ODS column (5 μm, 4.6 × 250 mm, Eicom) using citrate buffer 0.07 mol litre^{-1} with octane-sulphonic acid 1.5 mmol litre^{-1}, EDTA 30 μmol litre^{-1}, 15 % methanol (pH 3.9) as the mobile phase at a flow rate of 1.0 ml min^{-1}. The compounds were measured by electrochemical detection using a glassy carbon working electrode set at +700 mV against a silver–silver chloride reference electrode. The detection limit for each of the compounds was about 1 pg per sample. In some experiments, dopamine was separated on an Eicompak CA-5ODS column (5 μm, 4.6 × 250 mm, Eicom) using phosphate buffer 0.1 mol litre^{-1} with octane-sulphonic acid 5.8 mmol litre^{-1}, EDTA 0.3 mmol litre^{-1}, 20 % methanol (pH 6.0) as a mobile phase (flow rate 1.0 ml min^{-1}). The working electrode was set at +400 mV against a silver–silver chloride reference electrode and this gave a detection limit for dopamine of about 500 fg per sample.

Drugs

Drugs used were midazolam (Dormicum, Yamanouchi Pharmaceutical Co., Ltd), flunitrazepam (Rohypnol, Nippon Roche), flumazenil (Ro 15-1788, Hoffmann-La Roche), sulpiride (Dogmatyl, Fujisawa Pharmaceutical Co., Ltd) and tetrodotoxin (Sigma). Drugs were diluted in 0.9 % saline solution for i.v. injections, in Ringer solution for intraventricular injections or added to the perfusion medium for 20 min for intracerebral administration.

Histology

At the end of an experiment, the rat was anaesthetized deeply with pentobarbitone and perfused transcardially with 10 % formalin. The brains were removed, sectioned (50 μm) and stained with cresyl violet to facilitate probe location.

Statistical analysis

All values were expressed as a percentage of baseline and analysed using either paired t test or two-way analysis of variance (ANOVA), as appropriate. Statistical significance was assumed at $P < 0.05$.

RESULTS

The basal concentrations of dopamine, DOPAC and HVA in the dialysate were 9.0 (SEM 1.8) pg/20 min ($n = 6$), 622 (124) pg/20 min and 405 (92) pg/20 min, respectively. The concentrations required 4 h to stabilize after probe insertion, but were then unaffected by saline 1 ml i.v. and remained stable for at least a further 4 h (data not shown). Tetrodotoxin

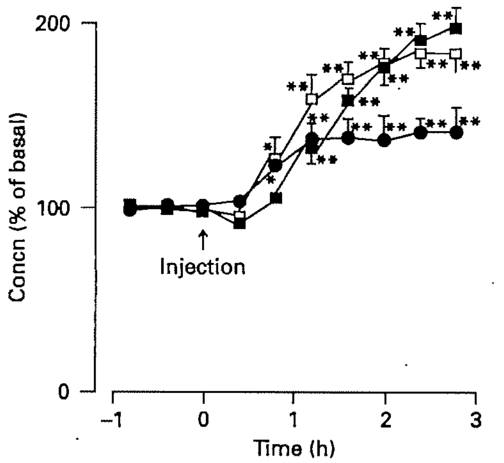


FIG. 3. Effects of i.v. injection of sulpiride 10 mg kg^{-1} on the concentrations of dopamine (●), DOPAC (□) and HVA (■) in striatal dialysates (mean, SEM of data from six rats). $^{*}P < 0.05$; $^{**}P < 0.01$ compared with value just before administration of sulpiride (paired *t* test).

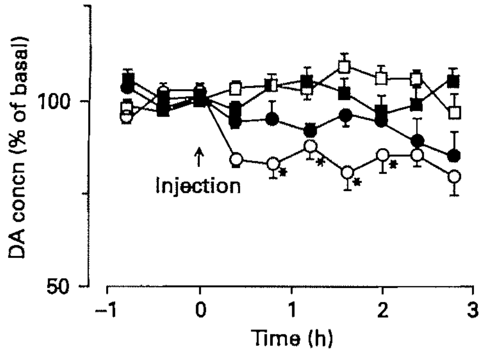


FIG. 4. Effects of midazolam and flumazenil on the concentrations of dopamine (DA) in striatal dialysates (mean, SEM of data from six rats). ● = Midazolam 0.075 mg kg^{-1}; ○ = midazolam 0.15 mg kg^{-1}; □ = flumazenil 6 µg kg^{-1}; ■ = midazolam 0.15 mg kg^{-1} + flumazenil 6 µg kg^{-1}. $^{*}P < 0.05$ compared with value just before administration of drugs (paired *t* test).

2 µmol $litre^{-1}$ infused into the striatum via the dialysis probe reduced basal concentrations of dopamine to approximately 20 % of control (fig. 2).

Sulpiride 10 mg kg^{-1} i.v. increased concentrations of dopamine, DOPAC and HVA in the striatal dialysate. Their values at 3 h after injection were approximately 140 %, 180 % and 200 % of control, respectively (fig. 3).

Midazolam 0.075 mg kg^{-1} and 0.15 mg kg^{-1} i.v. decreased concentrations of dopamine in striatal dialysates in a dose-dependent manner (fig. 4); the overall reductions during a 3-h observation period were 9 % and 17 %, respectively. However, midazolam did not significantly alter the concentrations of DOPAC and HVA (data not shown). The effects of midazolam 0.15 mg kg^{-1} were prevented by co-administration of flumazenil 6 µg kg^{-1}, a benzodiazepine receptor antagonist ($P < 0.01$, two-way ANOVA). Flumazenil alone did not affect concentrations of dopamine, DOPAC and HVA in striatal dialysates. Flunitrazepam 0.15 mg kg^{-1} and 0.03 mg kg^{-1} i.v. also decreased the concentrations of dopamine in striatal dialysates in a dose-related manner (fig. 5); the overall reductions during a 3-h observation period were 8 % (0.015 mg kg^{-1}) and 24 % (0.03 mg kg^{-1}), and tended to decrease concentrations of DOPAC and HVA (data not shown). The peak effects occurred approximately 100 min after injection of flunitrazepam (fig. 5) and were prevented ($P < 0.01$, two-way ANOVA) by co-administration of flumazenil 6 µg kg^{-1}.

A 20-min infusion of flunitrazepam 10 µmol $litre^{-1}$ into the striatum via the dialysis probe significantly reduced (26 % at peak) dialysate concentrations of dopamine for more than 1 h, but similar infusions of midazolam (10 and 100 µmol $litre^{-1}$) were ineffective (fig. 6); midazolam 1 mmol $litre^{-1}$ was also ineffective (data not shown). Neither compound affect striatal dopamine release when infused into the ipsilateral substantia nigra, via a dialysis probe, in a concentration of 100 µmol $litre^{-1}$ (fig. 6). However, midazolam 10 and 100 µmol $litre^{-1}$ infused simultaneously into both sites (striatum and the ipsilateral substantia nigra) or injected into the lateral ventricle (0.5 µg and 1 µg in 5 µl) reduced the concentrations of dopamine in striatal perfusates in a dose-dependent manner (fig.7). The peak reductions in dopamine concentration after simultaneous infusion of midazolam into both the striatum and substantia nigra were 14 % (10 µmol $litre^{-1}$) and 27 % (100 µmol $litre^{-1}$); and peak reductions after injection of midazolam into the lateral ventricle were 14 % (0.5 µg) and 22 % (1 µg).

DISCUSSION

The sodium channel blocker, tetrodotoxin has been used extensively in brain microdialysis experiments to demonstrate that the neurotransmitter and its metabolites detected in the perfusates have been released by action potential-induced depolarization and not released passively as a result of local tissue damage [18]. In the present study, approximately 80 % of the dopamine release was prevented by tetrodotoxin, indicating that it was caused mainly by neural activity.

I.v. midazolam and flunitrazepam decreased striatal dopamine release in a dose-dependent manner, in agreement with an earlier diazepam study [8]. Flunitrazepam was more effective than midazolam in doses similar to those used clinically to produce i.v. sedation and anaesthesia [19–21]. Concentrations of metabolites (DOPAC and HVA) in striatal dialysates tended to decrease after flunitrazepam, but were not affected by i.v. administration of midazolam. This lack of effect on the metabolites can be explained by the fact that the basal extracellular concentrations of DOPAC and HVA were 70 and 45 times greater than the concentration of dopamine; thus it can be assumed that a small (about 20 %) reduction in dopamine release induced by midazolam and flunitrazepam might not be sufficient to change the concentrations of the metabolites. The lack of effect, however, could not be caused by the methodological difficulties in measuring the metabolites as sulpiride, a drug reported to increase the extracellular concentration of dopamine, DOPAC and HVA by block of dopaminergic D_2 autoreceptors, increased the concentrations of these compounds to values similar

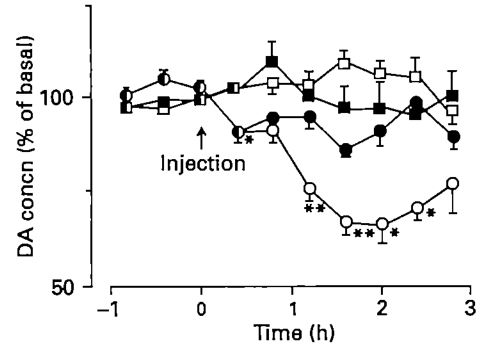


FIG. 5. Effects of flunitrazepam and flumazenil on the concentrations of dopamine (DA) in striatal dialysates (mean, SEM of data from six rats). ● = Flunitrazepam 0.015 mg kg^{-1}; ○ = flunitrazepam 0.03 mg kg^{-1}; □ = flumazenil 6 μg kg^{-1}; ■ = flunitrazepam 0.03 mg kg^{-1} + flumazenil 6 μg kg^{-1}. $*P < 0.05$, $**P < 0.01$ compared with value just before administration of drugs (paired t test).

to those reported previously [22]. The findings of the present study with midazolam and flunitrazepam suggest that, in the dose range used clinically, flunitrazepam had more pronounced effects on dopaminergic pathways than midazolam. These effects of midazolam and flunitrazepam were mediated by the $GABA_A$–benzodiazepine receptor complex, which inhibits the dopaminergic neuronal activity, because they were abolished by flumazenil.

As the striatum is known to be a terminal area of the dopaminergic neurones that arise from the substantia nigra, and their activities are controlled by the GABAergic inhibitory neurones, we were interested in examining the brain site responsible for the ability of the benzodiazepines to reduce the striatal dopamine release. To determine if systemically administered midazolam and flunitrazepam reduced striatal dopamine release by action in the terminal field (striatum) or in the cell body region (substantia nigra) of the nigrostriatal dopaminergic neurones, the compounds were applied directly to these structures by infusion through dialysis probes. Small concentrations of flunitrazepam infused into the striatum were effective, whereas larger concentrations infused into the substantia nigra were ineffective. This suggests that flunitrazepam reduced dopamine release by action at $GABA_A$–benzodiazepine receptors in the terminal field of the dopaminergic pathways. For midazolam to reduce striatal dopamine release, it was necessary to stimulate $GABA_A$–benzodiazepine receptors in both the terminal and cell body regions of the dopaminergic neurones by infusing it into both the striatum and substantia nigra simultaneously or by giving it intraventricularly. The effects of midazolam and flunitrazepam were antagonized by flumazenil, but this does not exclude the possibility that the two compounds were acting on different receptor subtypes [23], because flumazenil is not selective. Regional differences in the effects of benzodiazepines on dopamine release have been shown previously

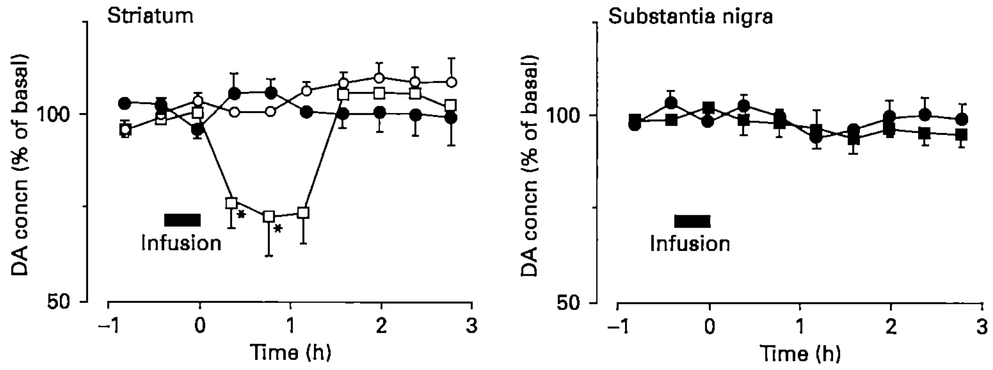


FIG. 6. Effects of infusion of midazolam 10 μmol $litre^{-1}$ (○) or 100 μmol $litre^{-1}$ (●) and flunitrazepam 10 μmol $litre^{-1}$ (□) or 100 μmol $litre^{-1}$ (■) into either the striatum (left) or ipsilateral substantia nigra (right) on concentrations of dopamine (DA) in striatal dialysates (mean, SEM of data from six rats). $*P < 0.05$ compared with value just before administration of drugs (paired t test).

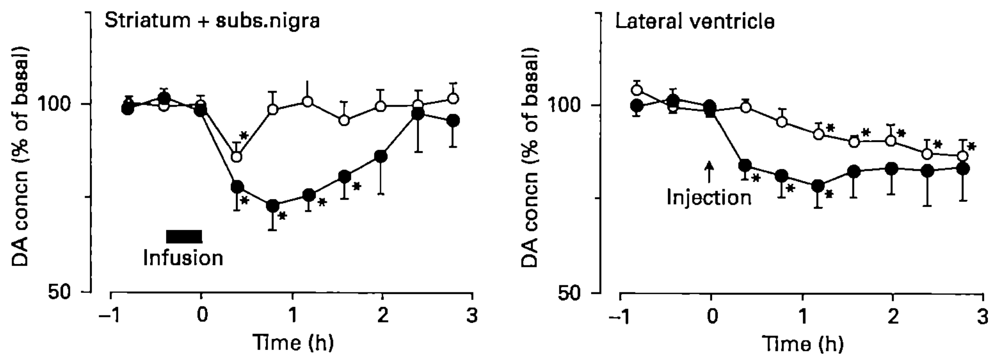


FIG. 7. Effects of infusion of midazolam 10 μmol $litre^{-1}$ (○) or 100 μmol $litre^{-1}$ (●) into both the striatum and ipsilateral substantia nigra (left) and injection of midazolam 0.5 μg 5 μl^{-1} (○) or 1.0 μg 5 μl^{-1} (●) into the lateral ventricle (right) on the concentrations of dopamine (DA) in striatal dialysates (mean, SEM of data from six rats). $*P < 0.05$ compared with value just before administration of midazolam (paired t test).

with systemic and central injections of diazepam and flurazepam which reduced dopamine release in the nucleus accumbens more than in the striatum [8, 10]. These regional differences can be explained by assuming a reduced basal GABA tone or more efficient receptor coupling in the nucleus accumbens and, therefore, more scope for a benzodiazepine effect in the structure. These two possibilities (regional differences in GABA tone and receptor coupling) may also explain the regional differences between the effects of midazolam and flunitrazepam observed in the present study.

ACKNOWLEDGEMENTS

This work was supported by a Grant for Scientific Research from the Ministry of Education, Science and Culture (Japan). Gifts of compounds from Hoffmann-La Roche and Yamanouchi are greatly appreciated.

REFERENCES

1. Wood PL. Actions of GABAergic agents on dopamine metabolism in the nigrostriatal pathway of the rat. *Journal of Pharmacology and Experimental Therapeutics* 1982; **222:** 674–679.
2. Scheel-Krüger J. Dopamine-GABA interactions: evidence that GABA transmits, modulates and mediates dopaminergic functions in the basal ganglia and the limbic system. *Acta Neurologica Scandinavica* 1986; 37 (Suppl. 107): 1–49.
3. Brose N, O'Neill RD, Boutelle MG, Fillenz M. Dopamine in the basal ganglia and benzodiazepine-induced sedation. *Neuropharmacology* 1988; **27:** 589–595.
4. Sadoval MRL, Palermo-Neto J. Behavioral aspects of GABAergic-dopaminergic interactions in the central nervous system. *European Journal of Pharmacology* 1989; **167:** 117–125.
5. Sperber EF, Wurpel JND, Sharpless NS, Moshe SL. Intranigral GABAergic drug effects on striatal dopamine activity. *Pharmacology Biochemistry and Behaviour* 1989; **32:** 1067–1070.
6. Reid M, Herrera-Marschitz M, Hökfelt T, Terenius L, Ungerstedt U. Differential modulation of striatal dopamine release by injection of γ-aminobutyric acid (GABA), dynorphin A and substance P. *European Journal of Pharmacology* 1988; **147:** 411–420.
7. Reid MS, Herrera-Marschitz M, Hökfelt T, Linderfors N, Persson H, Ungerstedt U. Striatonigral GABA, dynorphin, substance P and neurokinin A modulation of nigrostriatal dopamine release: evidence for direct regulatory mechanisms. *Experimental Brain Research* 1990; **82:** 293–303.
8. Invernizzi R, Pozzi L, Samanin R. Release of dopamine is reduced by diazepam more in the nucleus accumbens than in the caudate nucleus of conscious rats. *Neuropharmacology* 1991; **30:** 575–578.
9. Finlay JM, Damsma G, Fibiger HC. Benzodiazepine-induced decreases in extracellular concentrations of dopamine in the nucleus accumbens after acute and repeated administration. *Psychopharmacology* 1992; **106:** 202–208.
10. Zetterström T, Fillenz M. Local administration of flurazepam has different effects on dopamine release in striatum and nucleus accumbens: a microdialysis study. *Neuropharmacology* 1990; **29:** 129–134.
11. Costa E, Guidotti A. Molecular mechanism in the receptor action of benzodiazepines. *Annual Review of Pharmacology and Toxicology* 1979; **19:** 531–545.
12. Olsen RW. GABA–benzodiazepine–barbiturate receptor interactions. *Journal of Neurochemistry* 1981; **37:** 1–13.
13. Squires RF. Benzodiazepine receptors. In: Lajtha A, ed. *Handbook of Neurochemistry*. New York: Plenum, 1984; 261–301.
14. Gerfen CR, Herkenham M, Thibault J. The neostriatal mosaic II: patch- and matrix-directed mesostriatal dopaminergic and non-dopaminergic systems. *Journal of Neuroscience* 1987; **7:** 3915–3934.
15. Paxinos G, Watson C. *The Rat Brain in Stereotaxic Coordinates*. New York: Academic Press, 1986.
16. Benveniste H, Hansen AJ, Ottosen NS. Determination of brain interstitial concentration by microdialysis. *Journal of Neurochemistry* 1989; **52:** 1741–1750.
17. Lindefors N, Amberg G, Ungerstedt U. Intracerebral microdialysis. I. Experimental studies of diffusion kinetics. *Journal of Pharmacological Methods* 1989; **22:** 141–156.
18. Westerink BHC, Tuntler J, Damsma G, Rollema H, De Vries JB. The use of tetrodotoxin for the characterization of drug-enhanced dopamine release in conscious rats studied by brain dialysis. *Naunyn-Schmiedeberg's Archives of Pharmacology* 1987; **336:** 502–507.
19. Whitwam JG, Al-Khudhairi D, McCloy RF. Comparison of midazolam and diazepam in doses of comparable potency during gastroscopy. *British Journal of Anaesthesia* 1983; **55:** 773–777.
20. Dixon RA, Bennett NR, Harrison MJ, Kenyon C, Thornton JA. I.v. flunitrazepam and i.v. diazepam in conservative dentistry. *British Journal of Anaesthesia* 1980; **52:** 517–526.
21. Iisalo E, Kanto J, Aaltonen L, Mäkelä J. Flunitrazepam as an induction agent in children. *British Journal of Anaesthesia* 1984; **56:** 899–902.
22. Westerink BHC, De Vries JB. On the mechanism of neuroleptic induced increase in striatal dopamine release: brain dialysis provides direct evidence for mediation by autoreceptors localized on nerve terminals. *Neuroscience Letters* 1989; **99:** 197–202.
23. Doble A, Martin IL. Multiple benzodiazepine receptors: no reason for anxiety. *Trends in Pharmacological Sciences* 1992; **13:** 76–81.

British Journal of Anaesthesia 1993; 70: 186–191

MATHEMATICAL ANALYSIS OF THE UPPER RESPIRATORY TRACT FROM AN ANTHROPOMETRIC STUDY

G. JANVIER, L. BORDENAVE, P. REVEL, W. ELLISON, A. M. CROS AND S. WINNOCK

SUMMARY

In order to design a new, preformed tracheal tube adapted to the shape of the upper respiratory tract, we have undertaken an anthropometric study from lateral x-rays of the neck in 130 patients with the head in a fixed position. In order to assess different clinical situations, we studied three groups of patients: group 1 = sitting, no tracheal tube; group 2 = supine, no tracheal tube; group 3 = supine, trachea intubated. We defined a standard co-ordinate system and determined mathematical curves for segments of the upper respiratory tract by a polynomial regression method. With these data it was possible to study the effects of physiological variations on the shape of the curves. It was then possible to determine at which region changes occur and the factors influencing these changes. We found that the relative position of the larynx was constant, whereas the hypopharynx exhibited the greatest change with the position of the head. These observations should allow us to construct a new, preformed tracheal tube with elastic compliance properties to fit the changes occurring in the region of the hypopharynx. (Br. J. Anaesth. 1993; **70**: 186–191)

KEY WORDS

Airway: anatomy. Anatomy: mathematical analysis.

Prolonged nasal intubation is complicated by laryngeal lesions in a small number of patients [1]. These are produced by mechanical contact and abrasion at the level of the posterior laryngeal commissure [2, 3]. The semilunar shape of tracheal tubes exerts pressure almost exclusively on the posterior laryngeal area and forces the structure backwards. Movement of the larynx during swallowing causes friction in this area. Modification of the angle at which the tracheal tube enters the larynx may limit contact with the posterior larynx.

The first breakthrough was the introduction of polyvinylchloride tubes with thermal deformation properties. This material has improved laryngeal tolerance of tracheal tubes. However, the rate of deformation of the tube is gradual, and contact pressures are still sufficient to cause ulcers.

A second, more sophisticated, approach was the design of a preformed tube by the Swedish School of Uppsala. This tube was designed with a distal part fitting the laryngotracheal airway. In order to limit the pressure of the tube on the posterior commissure of the larynx, the shape was designed using standard anatomical features of the upper airway. Unfortunately, these tubes produced other problems (positioning problems, pharyngeal intolerance). Indeed, apart from the designers and promoters, few anaesthetists have used this tube.

It is possible that this failure may be explained by poor material conformation to the upper airway and failure of a model based on standard anatomical features.

We have undertaken a mathematical analysis of the pharyngolaryngeal anatomy of the airway based on radiological data and determined the most variable area of the upper airway as a function of factors such as cervicocephalic angulation, height, gender and age.

The goal of this work is to design a new tube in a material which adapts to upper airway morphology, in order to limit further the frequency of post-intubation laryngeal lesions.

PATIENTS AND METHODS

The study was approved by the Ethics Committee of Bordeaux University of Medicine, in accordance with the Helsinki Declaration. The patients studied were taken from three different departments: general surgery, traumatology and otorhinolaryngology.

Lateral cervicocephalic x-rays were taken with the same enlargement and corrected to actual size. For each examination, the patient's head was maintained in a fixed predetermined position by a frame which enabled us to adjust the plane of view with respect to a vertical line. The plane of view was either horizontal or vertical, depending on the patient group.

We studied three groups of adult patients:

Group 1 (sitting) consisted of 30 conscious patients (department of otorhinolaryngology) in the sitting position. In this group, the plane was horizontal.

G. JANVIER, M.D.; P. REVEL, M.D.; A. M. CROS, M.D.; S. WINNOCK, M.D.; Department of Anaesthesiology, Hospital Pellegrin, Bordeaux, France. L. BORDENAVE, INSERM U306, Bordeaux, France. W. ELLISON, PH.D., CNRS, University, Bordeaux I, France. Accepted for Publication: August 18, 1992.

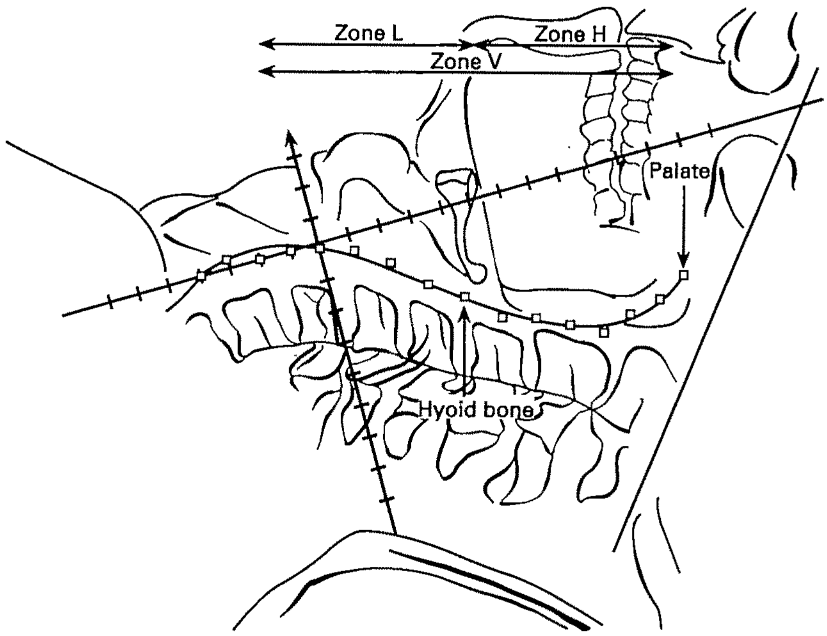


FIG. 1. X-ray-derived diagram of the cervicocephalic region showing the co-ordinate system and the three relevant zones.

TABLE I. *Subdivision of the three groups of patients according to cervicocephalic angle* (θ). *Group 1 = sitting position, no tracheal tube; group 2 = supine position, no tracheal tube; group 3 = supine position, trachea intubated*

	Subgroup			
	$\theta 1$	$\theta 2$	$\theta 3$	$\theta 4$
Group 1				
Min. angle	35	43	53	—
Max. angle	47	53	69	—
Mean angle	43.5	48.4	60.1	—
SD	5.1	4.8	5.1	—
Group 2				
Min. angle	19	34	44	—
Max. angle	33	42	60	—
Mean angle	25.1	37.5	50.2	—
SD	4.4	2.6	4.7	—
Group 3				
Min. angle	7	31	43	55
Max. angle	29	42	54	70
Mean angle	21.5	36.6	48.4	56.2
SD	7.3	3.6	3.9	8.5

Group 2 (supine position, non-intubated trachea) consisted of 70 conscious patients (department of traumatology) in the supine position. All the patients had bone fractures of the lower part of the body; patients with trauma to the upper body were excluded. In this group, the plane was vertical (perpendicular to the table).

Group 3 (supine position, trachea intubated and lungs ventilated) consisted of 30 anaesthetized patients (department of general surgery) with a nasotracheal tube. In this group the plane was vertical (perpendicular to the table).

All tracheal intubations were with Portex Blue Line tracheal tubes.

For each x-ray the same orthogonal co-ordinate system was used to trace the shape of the pharyngolaryngeal airway. The co-ordinate axes were defined as follows: the Y axis was the prolongation of the line passing through the upper plane of the vertebral body of the 6th cervical vertebra (C6); the X axis was the line perpendicular to the Y axis and passing through the lower posterior part of the subglottic radio translucency at the C6 level (fig. 1).

Each x-ray was defined with respect to these axes. The points which define the curve of the upper airway were chosen on the posterior wall of the airway. The curve representing the shape of the pharyngolaryngeal airway was obtained by measuring the airway co-ordinates at 1-cm intervals along the X axis, starting at the upper face of C6 and continuing to the bony palate. The upper face of C6 was chosen to define the Y axis because it is situated just below the vertebral body of C5 which, in the adult, is at the same level as the glottis. Moreover, in the median plane, the region C6–7 is in a zone which is inflexible. Thus the co-ordinate axes are not modified by possible extreme lordosis or "straight neck".

The zones studied (fig. 1) were:

Zone L. The region between the upper face of C6 and the projection of the large horn of the hyoid bone on the airway. This region corresponds to the larynx.

Zone H. The region between the hyoid bone and the bony plane of the palate. This region corresponds to the hypopharynx.

Zone V. The region between C6 and the palate, which corresponds to the upper airway.

The set of curves for the same zone varied considerably. This is a reflection of the individual morphological variations in each of the three groups. Consequently, and in accordance with data in the literature [4–7], certain factors were taken into account. These were:

The cervicocephalic angle (the angle between Y axis and the straight line passing by the orbital floor and the external occipital protuberance). This is a good index of individual anatomical variations in cervical rotation. In each of the three groups, the cervicocephalic angle covered a wide range of values and it was necessary to divide the angles into three or four homogenous subgroups (table I).

The subject's height. The patients were classified into two subgroups according to body height: subgroup T1 = patients of height less than 1.65 m (mean 1.6 (SD 0.03) m); subgroup T2 = those of height greater than 1.65 m (mean 1.72 (0.03) m). The mean height of all patients was 1.66 (0.06) m.

The subject's gender.

The subject's age. Patients were classified into two subgroups: subgroup A1 = patients younger than 50 yr (mean 32 yr, range 18–60 yr; subgroup A2 = patients older than 50 yr (mean 68 yr, range 61–87). The mean age for all patients was 53 yr.

X-rays were analysed as follows. First we describe the shape of each of the upper airway curves by a polynomial regression technique. The entire upper airway zone V is well approximated by a cubic polynomial and when the analysis is restricted to either zone L or H, the "best" cubic polynomial has the coefficient of X^3 equal to zero—that is, it is a quadratic polynomial. In all cases, the correlation coefficient for the polynomial regression was > 0.95. This indicates that all the experimental curves were well approximated by the polynomials. Thus we can say that the shape of an upper airway curve in the zones V, L and H can be described adequately by a polynomial of maximum degree of 3.

The second step was to compare the curves for each of the three groups of subjects and the four variation factors in the three zones L, H and V. We chose to use the area between the curve and the X axis as an indicator. The area was calculated from the polynomial equation defining the curve in the zone L, H or V. If two curves are the same, then the areas are the same; if areas are not the same, the two curves are different; if two areas are the same, one cannot conclude anything about the curves. This relatively crude indicator was sufficient for our purposes according to the following reasoning: in a random group of subjects in identical clinical situations, there are wide differences in the cervicocephalic angle; there is a statistically significant correlation between the cervicocephalic angle and the area under the curve. Large differences in the areas in zone H imply differences in the curves.

Thus one can say that in a clinically homogeneous group of subjects there are large variations in the morphology of the upper airway in the zone H and no "standard" model exists.

RESULTS

Shape of the averaged curves

The average curve of all three groups for zone V is shown in figure 2. When the curves of each group are considered separately, major variations become apparent (fig. 3). The difference in the subject's position (supine or sitting), whilst the head is maintained in an apparently controlled position (i.e. horizontal or vertical, depending on the groups), is responsible for these differences.

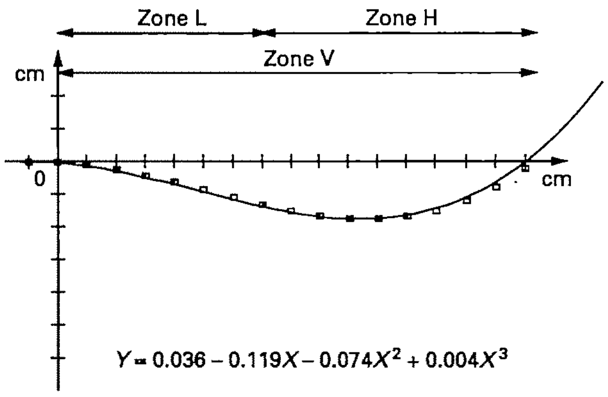


FIG. 2. Airway morphology obtained from all data (curve is the average for all subjects). The three anatomical zones are indicated by arrows.

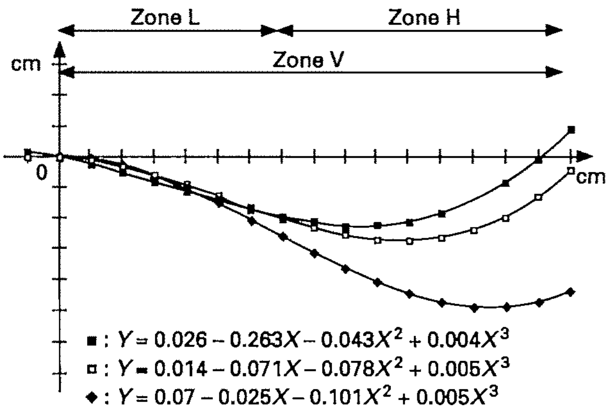


FIG. 3. Representation of the morphology of the upper airway for each of the three groups. Sitting position, no tracheal tube (◆); mean value of the cervicocephalic angle (θ) = 56°. Supine position, no tracheal tube (□); mean value of $\theta = 39°$. Supine position, trachea intubated (■); mean value of $\theta = 38°$.

Variable factors

Cervicocephalic angle. Data on cervicocephalic angle for the subgroups within each of the three groups of patients are summarized in table II. Figures 4–6 illustrate the large variability in

TABLE II. *Mean* (SD) *cervicocephalic angle* (θ) *and area between curve segments and the* X *axis for the cervicocephalic angle subgroups.* n = *No. patients. Group 1 = sitting position, no tracheal tube; group 2 = supine position, no tracheal tube; group 3 = supine position, trachea intubated*

	n	Angle (deg.)	Area (cm²)
Group 1			
Subgroup $\theta 1$	10	43.5 (5.1)	24
Subgroup $\theta 2$	10	48.4 (4.8)	34
Subgroup $\theta 3$	10	60.1 (5.1)	71
Mean		56 (12)	65
Group 2			
Subgroup $\theta 1$	24	25.1 (4.4)	17
Subgroup $\theta 2$	24	37.5 (2.6)	51
Subgroup $\theta 3$	22	50.2 (4.7)	51
Mean		39.6 (12)	33
Group 3			
Subgroup $\theta 1$	7	25.5 (7.3)	10
Subgroup $\theta 2$	7	36.6 (3.6)	14
Subgroup $\theta 3$	8	48.4 (3.9)	34
Subgroup $\theta 4$	8	56.2 (8.5)	42
Mean		38.6 (14.1)	26

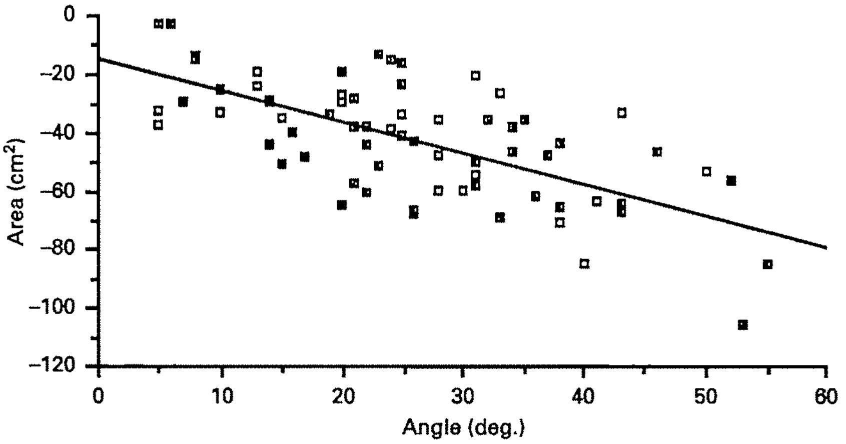


FIG. 4. Representation of correlation between cervicocephalic angle and area under curve for group 2 (supine, no tracheal tube) in zone V. $y = -14.6419-1.072x$; $r = 0.66$.

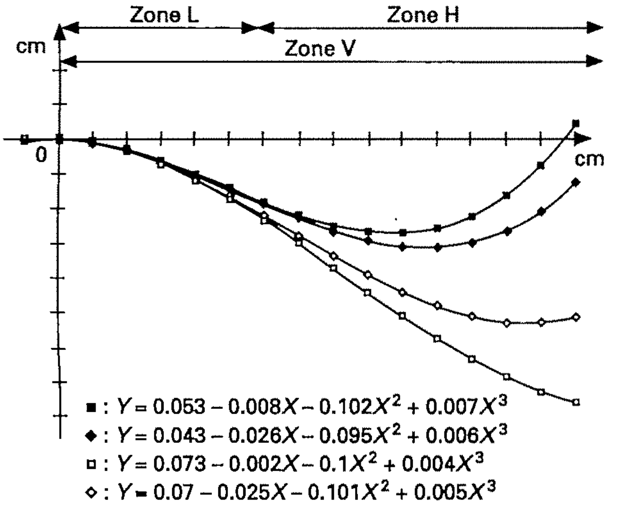


FIG. 5. Representation of the morphology of the upper airway of group 1 (sitting position, no tracheal tube) which is subdivided into three subgroups. Subgroup $\theta 1$ (■): mean value of the cervicocephalic angle (θ) = 43°; subgroup $\theta 2$ (◆): mean value of $\theta = 48°$; subgroup $\theta 3$ (□): mean value of $\theta = 60°$. For all patients in group 1 (◇): mean value of $\theta = 56°$.

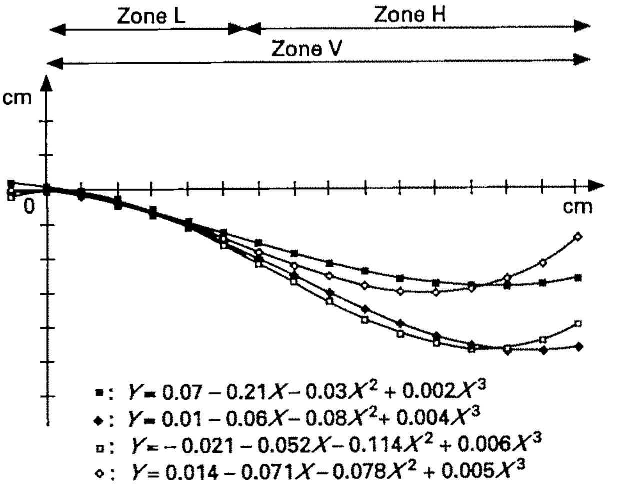


FIG. 6. Representation of the morphology of the upper airway of group 2 (supine position, no tracheal tube) which is subdivided into three subgroups. Subgroup $\theta 1$ (■): mean value of the cervicocephalic angle $\theta = 25°$; subgroup $\theta 2$ (◆): mean value of $\theta = 37°$; subgroup $\theta 3$ (□): mean value of $\theta = 50°$. For all patients in group 2 (◇), mean value of $\theta = 39°$.

TABLE III. *Values of r and their significance (P) in each zone for each variation factor for the whole population group (sitting, supine, intubated and non-intubated)*

	Angle	Height	Sex	Age
Zone L				
r	−0.33	0.22	−0.07	0.07
P	< 0.05	ns	ns	ns
Zone H				
r	−0.52	−0.01	0.19	−0.47
P	< 0.01	ns	ns	< 0.01
Zone V				
r	−0.66	−0.11	0.33	−0.39
P	< 0.01	ns	ns	< 0.05

TABLE IV. *Height- and age-related variations in area between the curve segments and the X axis for whole population*

	Height			Age		
	H1	H2	Mean	A1	A2	Mean
Area (cm²)	17	25	24	15	38	26

pharyngolaryngeal anatomy. The hypopharynx zone is greatly influenced by the values of the cervicocephalic angle.

There was a significant linear correlation between the cervicocephalic angle and the area under the curve. This is illustrated in figure 4 for zone V for group 2 and summarized in table III.

Height. There was no significant correlation between heights of the subjects and the areas under the corresponding curves (table IV). For groups H1 and H2, there was no significant difference between the mean values of the areas.

Gender. There were no statistically significant differences between the area for males and females.

Age. There was a statistically significant correlation between the areas under the curves and the patient's ages (table IV). For the two groups A1 and A2, the difference in the mean areas was significant for zones H and V and non-significant for zone L.

The relative importance of each of the factors on the morphology of the three regions is summarized in table III. In terms of the correlation coefficient, *r*, the cervicocephalic angle is of primary importance. It is in the hypopharynx that the significance is largest; in the larynx, L, the significance is weaker. A relatively good correlation exists between age and morphology of the hypopharynx. However, in this study, we found no significant correlation between height or gender and morphological variations.

DISCUSSION

The object of the study was to demonstrate the existence of variations in a mathematical representation of the pharyngolaryngeal airway in subjects with different body positions, but with the head always positioned in the same way, perpendicular and midline with respect to the frontal body plane. This representation allowed us to identify zones where there were morphological variations as a function of individual anthropometric characteristics.

A possible criticism of this study is that we analysed radiographs in only one plane (profile). Thus it was not possible to obtain a three-dimensional representation for the intubated group. It is well known that a tracheal tube is never in a perfectly median position at the level of the larynx.

Other techniques could have overcome this difficulty, for example computed tomography. Our choice of technique was dictated by economic considerations and by the technical inability to maintain the tubes in reproducible positions. This study has described the shape of the upper respiratory tract in one fixed position of the head; in this respect, it can be considered as a preliminary study which requires further investigations, with different fixed cervicocephalic angles and, ultimately, a dynamic analysis.

A second criticism is the choice of the co-ordinate axes. The Y axis is not situated on any laryngeal structure. It would have been preferable to fix the origin of the axes at some point of the upper respiratory tract. However, taking into account the low mobility of the larynx with respect to the spinal column, our origin is valid [4]. Moreover, our origin is defined in terms of bony structures of the spinal column which are more easily identified on radiographs, than the upper airway.

A third criticism is our choice of using the areas under curve segments to compare the shapes of the segments. If the areas are different, then the curves are different. The converse, of course, is not necessarily true. As the areas in some zones were significantly different, it follows that the shapes of the curves were significantly different, which is sufficient for our purposes.

In spite of these criticisms, the study enabled us to answer some important questions. First, it is not possible to define a unique, "standard" model of the upper laryngeal airway. We have shown that the airway consists of two very different regions: one has a morphology which varies little (larynx), the other has a morphology with random variations (hypopharynx). The principal cause of modification in zone H is the structural change in the head as a function of body position. This influence has already been reported by Alexopoulos and his colleagues in their work on a new intubation device [8–13]. The changes in cervicocephalic angle imply significant deformations in the pharyngolaryngeal structures. There is great mobility in the vertebral segments of the spinal column in zone H; the anatomical representation of the larynx (zone L) is more constant. The small amplitude of movement and the rigidity of the thyroid cartilage are probably responsible for the small amount of variation in position of the larynx in the median plane. Obviously, our study cannot take into account the superoinferior movements of the larynx, because the radiographic analysis was static.

The anatomical variations are essentially interindividual. They are caused by changes in body position without the head being either in flexion or in hyperextension. This accentuates the opening or closing of the cervicocephalic angle and thus it is difficult to predict the position of the cervical spine and the upper airways as a function of head position.

The anatomical variations induced by the cervicocephalic angle are of prime importance in the change in position of the airway. Analysis of age showed that young adults have a more pronounced pharyngeal convexity than older subjects. This may be explained by greater suppleness of the tissues which surround the cephalic extremity. The other variables which we studied (gender, height) were less important in our population.

Any new type of intubation device which has minimum contact pressure in the larynx should be constructed of a material which deforms in the median plane and adapts to the anatomical variations observed in this study. This is particularly true for the hypopharyngeal region.

REFERENCES

1. Black A, Hatch D, Nauth-Misir N. Complications of nasotracheal intubation in neonates, infants and children: A review of 4 years' experience in children's hospital. *British Journal of Anaesthesia* 1990; **65**: 461–467.
2. Colice G, Stukel T, Dain B. Laryngeal complications of prolonged intubation. *Chest* 1989; **96**: 877–884.
3. Withed R. A prospective study of laryngotracheal sequelae in long-term intubation. *Laryngoscope* 1984; **94**: 367–377.
4. Penning L. Radioanatomy of upper airway in flexion and retroflexion of the neck. *Neuroradiology* 1988; **30**: 17–21.
5. Carlsöö S, Leijon G. A radiographic study of the position of the hyo-laryngeal complex in relation to the skull and the cervical column in man. *Transactions of the Royal Dental Society* 1960; **5**: 14–34.
6. Bhalla S, Simmons E. Normal ranges of intervertebral-joint motion of the cervical spine. *Canadian Journal of Surgery* 1969; **12**: 181–187.
7. Sivarajan M, Fink R. The position and state of the larynx during general anesthesia and muscle paralysis. *Anesthesiology* 1990; **72**: 439–442.
8. Alexopoulos C, Lindholm CE. Airway complaints and laryngeal pathology after intubation with an anatomically shaped endotracheal tube. *Acta Anaesthesiologica Scandinavica* 1983; **27**: 339–344.
9. Eckerbom B, Lindholm CE, Alexopoulos C. Airway lesions caused by prolonged intubation with standard and anatomically shaped tracheal tubes. A post-mortem study. *Acta Anaesthesiologica Scandinavica* 1986; **30**: 366–373.
10. Lindholm CE. Experience with a new orotracheal tube. *Acta Otolaryngologica* 1973; **75**: 389–390.
11. Alexopoulos C, Larsson S, Lindholm CE. The anatomical

shape of the airway during endotracheal intubation. *Acta Anaesthesiologica Scandinavica* 1983; 27: 331–334.

12. Alexopoulos C, Larsson S, Lindholm CE. Anatomical shape of the airway. *Acta Anaesthesiologica Scandinavica* 1983; 27: 185–192.
13. Alexopoulos C, Larsson S, Lindholm CE. The conformity of an anatomically shaped endotracheal tube to the shape of the airway. *Acta Anaesthesiologica Scandinavica* 1983; 27: 335–338.

British Journal of Anaesthesia 1993; 70: 192–195

COMPARISON OF RECOVERY FROM ANAESTHESIA INDUCED IN CHILDREN WITH EITHER PROPOFOL OR THIOPENTONE

C. J. RUNCIE, S. J. MACKENZIE, D. S. ARTHUR AND N. S. MORTON

SUMMARY

We studied 102 children undergoing day-case surgery, allocated randomly to receive either thiopentone 5 mg kg^{-1} or propofol 3 mg kg^{-1} i.v. at induction of anaesthesia. They then inhaled nitrous oxide and halothane in oxygen until a larnygeal mask airway could be inserted. Thereafter, halothane was substituted by isoflurane and analgesia provided by regional nerve block. Recovery from anaesthesia was assessed by the time taken to reach clinically-defined criteria and by calculation of sedation, pain and vomiting scores. In children aged less than 5 yr, only the time to spontaneous eye opening was shorter after propofol induction ($P < 0.05$*). In children aged 5–11 yr, times of spontaneous eye opening, giving name and discharge were shorter after propofol induction (*$P < 0.05$*). These results indicate that propofol hastened early recovery in children undergoing day-case surgery, but earlier discharge occurred only in older children.* (Br. J. Anaesth. 1993; **70**: 192–195)

KEY WORDS

Anaesthesia: paediatric. Anaesthetics, Intravenous: propofol, thiopentone. Recovery.

Propofol has been used since 1984 in adult anaesthesia and has been shown to produce more rapid recovery than thiopentone. It has therefore become popular for day-case anaesthesia. Formal studies of recovery in adults have shown earlier return of clinical criteria of recovery, protective reflexes and psychomotor function after propofol induction [1]. If anaesthesia is maintained with halothane for more than 30 min, however, indices of recovery are similar whichever induction agent is used [2].

In children, early recovery is also more rapid after induction of anaesthesia with propofol than after thiopentone [3]. Recent studies have compared propofol for both induction and maintenance of anaesthesia with thiopentone induction and maintenance by volatile agent [4, 5]. Thus it is not known if induction of anaesthesia with propofol followed by inhalation maintenance in children enhances all aspects of recovery, allowing earlier discharge after day-case surgery. The aim of this study was to compare recovery after propofol and thiopentone induction in children having short general surgical procedures as day-cases with anaesthesia maintained by isoflurane and analgesia provided by local anaesthetic nerve block.

PATIENTS AND METHODS

The study was undertaken in the day-case unit of a regional paediatric hospital. We studied 102 patients, ASA grades I or II, anaesthetized for short general surgical procedures by two of the authors (D.S.A. and C.J.R. or D.S.A. and S.J.M.) after approval from the Hospital Ethics Committee and written informed parental consent. Children having procedures completed in the anaesthetic room (examination under anaesthesia or release of tongue-tie) were excluded. Patients were studied in two age groups: less than 5 yr and 5–11 yr inclusive.

Premedication comprised EMLA emulsion cream (lignocaine 25 mg g^{-1} and prilocaine 25 mg g^{-1}) applied to the dorsa of both hands at least 1 h before induction. Within each age group, patients were allocated randomly (by computer-generated random numbers) to receive either thiopentone 5 mg kg^{-1} or propofol 3 mg kg^{-1} i.v. Increments were given as required to allow the child to tolerate the face mask. Lignocaine 0.3 mg kg^{-1} was added to the propofol to reduce injection pain. All children then inhaled 67% nitrous oxide and an increasing concentration of halothane in oxygen via a Rees T-piece or Bain attachment. A laryngeal mask airway was inserted and an appropriate regional nerve block performed.

After transfer to theatre, all patients received 66% nitrous oxide and 1–1.5% isoflurane in oxygen for maintenance of anaesthesia. Isoflurane was discontinued as the dressings were applied and the laryngeal mask removed; patients were then given 100% oxygen and transferred to the recovery area in the lateral position with the operative site uppermost. Children remained in the recovery area until they could open the eyes spontaneously and they then returned to the adjacent recovery ward.

The following times were recorded by the anaesthetists: start of induction; start of surgery; iso-

---

COLIN J. RUNCIE, M.B., CH.B., M.R.C.P., F.R.C.ANAES.; SIMON J. MACKENZIE, M.B., CH.B., F.R.C.ANAES.; Division of Anaesthesia, Glasgow Royal Infirmary, Glasgow G31 3ER. DOUGLAS S. ARTHUR, M.B., CH.B., F.R.C.ANAES.; NEIL S. MORTON, M.B., CH.B., F.R.C.ANAES.; Division of Anaesthesia, Royal Hospital for Sick Children, Yorkhill, Glasgow. Accepted for Publication: August 5, 1992.

Correspondence to C.J.R.

TABLE I. *Patient characteristics (median (interquartile range)) and operative details*

	Age < 5 yr		Age 5–11 yr	
	Thiopentone ($n = 29$)	Propofol ($n = 27$)	Thiopentone ($n = 21$)	Propofol ($n = 26$)
Age (months)	38 (13–46)	35 (13–49)	87 (77–115)	76 (64–88)
Weight (kg)	14 (11–16)	15 (10–17)	22 (20–30)	21 (19–24)
Sex (M:F)	22:7	22:5	19:2	22:4
Operations				
Circumcision	16	10	8	10
Inguinal hernia repair/hydrocele	7	12	10	10
Periumbilical hernia repair	3	3	1	1
Regional blocks				
Caudal	17	11	8	10
Inguinal	6	11	10	10
Other	6	5	3	6
Anaesthesia time (min)	19 (14–21)	19 (17–21)	19 (15–23)	18 (13–21)
Surgery time (min)	10 (8–12)	9 (7–12)	10 (8–15)	10 (7–11)

TABLE II. *Recovery times (median (interquartile range)) and 95% confidence intervals for the differences between groups*

	Thiopentone	Propofol	95% confidence interval	P
Age < 5 yr				
Isoflurane off to eyes open (min)	21 (15–26)	17 (13–19)	1, 9	0.024
Eyes open to oral intake (min)	15 (3–38)	5 (4–8)	−1, 25	0.11
Eyes open to first analgesia (min)	40 (24–52)	33 (28–68)	−12, 20	0.9
Eyes open to discharge (min)	95 (77–125)	88 (74–111)	−7, 24	0.35
Age 5–11 yr				
Isoflurane off to eyes open (min)	20 (15–24)	16 (13–19)	0, 8	0.03
Isoflurane off to gives name (min)	30 (22–35)	20 (14–22)	4, 15	0.003
Eyes open to oral intake (min)	21 (9–58)	16 (10–26)	−3, 29	0.18
Eyes open to first analgesia (min)	49 (38–70)	39 (28–63)	−8, 27	0.2
Eyes open to discharge (min)	117 (88–158)	86 (70–105)	10, 50	0.004

flurane discontinued. Thereafter, patients were assessed by the recovery staff, unaware of the induction agent used, who recorded the following times: spontaneous eye opening; giving own name when asked; oral fluid intake; first analgesia; discharge. In addition, they assessed sedation, pain and vomiting by simple four-point scores at 0, 5, 15, 30, 60 and 90 min. Sedation was scored as eyes open spontaneously (1), to speech (2), to shake (3) and unrousable (4). Pain was scored as none (0), mild (1), moderate (2) and severe (3) and vomiting as none (0), nausea only (1), one vomit (2) and more than one vomit (3). For each child, an overall sedation score was calculated as the sum of the six scores obtained during the recovery period. Pain and vomiting scores were calculated similarly. Children were discharged when they were awake and alert, tolerating solids and mobilizing and communicating appropriately for their age.

Data were analysed statistically by the Mann–Whitney test (Minitab statistical software, Pennsylvania, U.S.A.). $P < 0.05$ was taken as significant.

RESULTS

For both age-groups, patient characteristics and operative details were comparable for the two induction agents (table I). The sole exception, in the older children, was that patients receiving propofol were significantly younger than patients receiving thiopentone, although their median weights were not significantly different. One patient in each age group suffered transient hypoxaemia ($Sp_{O_2} < 90\%$) during induction as a result of laryngospasm or breath-holding; each induction agent was involved in one incident.

Recovery times are detailed in table II. In the younger age group, early recovery (as indicated by

TABLE III. *Recovery scores (median (interquartile range)) and 95% confidence intervals for the differences between groups. For each child, scores are calculated as the sum of the six scores obtained during recovery in each category. ns = Not significant*

	Thiopentone	Propofol	95% confidence interval	*P*
Age < 5 yr				
Sedation score	13 (11.5–15)	12 (12–13)	0, 2	ns
Pain score	1 (0–3)	4 (0–5)	−3, 0	0.02
Vomiting score	0 (0–0)	0 (0–0)	0, 0	ns
Age 5–11 yr				
Sedation score	14 (12–15.5)	12 (12–14)	0, 2	ns
Pain score	3 (0.5–4)	2 (0–4)	−1, 2	ns
Vomiting score	0 (0–1)	0 (0–0)	0, 1	ns

the time from discontinuation of isoflurane to spontaneous eye opening) was more rapid after propofol. Other indices of recovery did not differ significantly between the two groups. In the older age group, times to spontaneous eye opening, giving name and discharge were shorter after propofol induction. Times to first oral intake and first analgesia did not differ significantly between groups, but there was a trend in favour of propofol.

In the younger children, postoperative pain scores were significantly greater after propofol (table III).

DISCUSSION

More rapid recovery after induction with propofol than after thiopentone has been well documented in adult outpatient anaesthesia, but not in children. This study was prompted by the authors' clinical impression that the benefits of propofol were less obvious in children and concern that its greater cost was therefore difficult to justify. Our aim was thus to compare propofol with the standard agent, thiopentone, as part of an anaesthetic technique in common use in this unit.

Possible weaknesses in our methodology include the sequential use of both halothane and isoflurane, the inclusion of children younger than 3 yr and significantly greater pain scores after operation in the young children after induction of anaesthesia with propofol. The literature on the recovery characteristics of halothane and isoflurane in children is complicated by induction with inhalation in most studies [6, 7]. In adults, however, spontaneous ventilation of halothane for 30 min after i.v. induction [2] abolished the improvement in recovery seen with propofol. We therefore hoped to avoid both this confounding factor and the airway irritability and desaturation during isoflurane induction [8] by administering halothane until surgical anaesthesia was reached and then changing to isoflurane [9].

Children younger than 3 yr were included as it was the authors' initial impression that the younger the child, the smaller were the differences between propofol and thiopentone. The safety of propofol in this age group has been well documented [10], as has this hospital's clinical experience [11–13]. As Puttick and Rosen have shown that recovery times are more sensitive than the Steward scoring system [4], we used only the former in this study.

The importance of the difference in pain scores between the two groups in younger children is unclear. An explanation for this difference may be that inguinal hernia and hydrocele operations were more common in the group receiving propofol. Children undergoing these procedures often require oral analgesia with paracetamol after operation for peritoneal pain, despite successful regional nerve block. The presence of pain is a possible explanation for the more rapid early recovery in younger children after propofol.

In children younger than 5 yr, only the time to spontaneous eye opening was shorter after propofol than after thiopentone induction. A trend in favour of propofol for other recovery times did not reach statistical significance. In children aged 5–11 yr, times of spontaneous eye opening, giving name and discharge were shorter after propofol. These results are in broad agreement with those of other studies. The degree to which our results can be generalized to paediatric outpatient anaesthesia for other procedures or using other techniques is not clear. Nevertheless, they do suggest that selective use of propofol in older children may allow increased throughput in paediatric day-case units, while moderating increases in cost.

REFERENCES

1. Sebel PS, Lowdon JD. Propofol: a new intravenous anesthetic. *Anesthesiology* 1989; **71**: 260–277.
2. Sanders LD, Isaac PA, Yeomans WA, Clyburn PA, Rosen M, Robinson JO. Propofol-induced anaesthesia. Double-blind comparison of recovery after anaesthesia induced by propofol or thiopentone. *Anaesthesia* 1989; **44**: 200–204.
3. Mirakhur RK. Induction characteristics of propofol in children: comparison with thiopentone. *Anaesthesia* 1988; **43**: 593–598.
4. Puttick N, Rosen M. Propofol induction and maintenance with nitrous oxide in paediatric outpatient dental anaesthesia. A comparison with thiopentone–nitrous oxide–halothane. *Anaesthesia* 1988; **43**: 646–649.
5. Borgeat A, Popovic V, Meier D, Schwander D. Comparison of propofol and thiopental/halothane for short-duration ENT surgical procedures in children. *Anesthesia and Analgesia* 1990; **71**: 511–515.
6. Fisher DM, Robinson S, Brett CM, Perin G, Gregory GA. Comparison of enflurane, halothane and isoflurane for diagnostic and therapeutic procedures in children with malignancies. *Anesthesiology* 1985; **63**: 647–650.
7. McAteer PM, Carter JA, Cooper GM, Prys-Roberts C. Comparison of isoflurane and halothane in outpatient paediatric dental anaesthesia. *British Journal of Anaesthesia* 1986; **58**: 390–393.
8. Sampaio MM, Crean PM, Keilty SR, Black GW. Changes in

oxygen saturation during isoflurane anaesthesia in children. *British Journal of Anaesthesia* 1989; 62: 199–201.
9. Pandit UA, Steude GM, Leach AB. Induction and recovery characteristics of isoflurane and halothane anaesthesia for short outpatient procedures in children. *Anaesthesia* 1985; 40: 1226–1230.
10. Valtonen M, Iisalo E, Kanto J, Tikkanen J. Comparison between propofol and thiopentone for induction of anaesthesia in children. *Anaesthesia* 1988; 43: 696–699.
11. Morton NS. Abolition of injection pain due to propofol in children. *Anaesthesia* 1990; 45: 70.
12. Morton NS, Johnston G, White M, Marsh BJ. Propofol in paediatric anaesthesia. *Paediatric Anaesthesia* 1992; 2: 89–97.
13. Cameron E, Johnston G, Crofts S, Morton NS. The minimum effective dose of lignocaine to prevent injection pain due to propofol in children. *Anaesthesia* 1992; 47: 604–606.

British Journal of Anaesthesia 1993; 70: 196–200

ACUTE HAEMODYNAMIC EFFECT OF SODIUM BICARBONATE IN CANINE RESPIRATORY OR METABOLIC ACIDOSIS

T. NISHIKAWA

SUMMARY

This study has examined the acute haemodynamic effects of 7% sodium bicarbonate solution 1 mmol kg^{-1} (1.2 ml kg^{-1}) administered into the right atrium over 5 s in 25 anaesthetized dogs allocated randomly to respiratory (arterial pH (pH$_a$) 7.18, Pa_{CO_2} 10.1 kPa (n = 8)) or metabolic acidosis (pH$_a$ 7.27, base deficit −9.0 mmol litre^{-1} (n = 7)) or metabolic neutrality (pH$_a$ 7.39 (n = 10)). The pH$_a$ and Pa_{CO_2} in the respiratory acidosis group differed from those in the two other groups ($P < 0.01$). One dog with respiratory acidosis developed progressive circulatory depression and cardiac arrest 6 min after injection of sodium bicarbonate. In the remaining seven dogs with respiratory acidosis, administration of sodium bicarbonate 1 mmol kg^{-1} produced transient decreases in mean arterial pressure, right ventricular dP/dt, and pulmonary blood flow, with increased right atrial pressure, followed by a gradual return of these variables to the baseline. The magnitude of reduction in pulmonary blood flow after sodium bicarbonate was greater in dogs with respiratory acidosis ($P < 0.05$) compared with the changes in the two other groups. The haemodynamic depression after bicarbonate was pronounced during respiratory acidosis and this may be attributed to a smaller pH$_a$ in the respiratory acidosis group, further reduction of intracellular pH, or both. It is suggested that when metabolic acidosis is corrected, bicarbonate should be administered with caution in the presence of respiratory acidosis. (Br. J. Anaesth. 1993; **70**: 196–200)

KEY WORDS

Acid–base equilibrium: metabolic acidosis, respiratory acidosis. Complications: hypercapnia. Pharmacology: sodium bicarbonate.

Sodium bicarbonate has been used widely for the treatment of metabolic acidosis during cardiopulmonary resuscitation [1–3], although its use during cardiopulmonary resuscitation has recently been questioned [4–8].

Sodium bicarbonate has been reported to cause reductions in arterial pressure and myocardial contractility, and often myocardial ischaemia after the i.v. injection [9–13]. A greater reduction in myocardial contractility has been reported during respiratory acidosis than during metabolic acidosis [14, 15], suggesting that intracellular carbon dioxide tension is more potent as a myocardial depressant than pH and bicarbonate concentration. Furthermore, several previous reports have indicated significant differences between the partial pressures of carbon dioxide in arterial and venous blood sampled from patients undergoing cardiopulmonary resuscitation or with circulatory failure (reduced and increased partial pressure of carbon dioxide in the arterial and venous blood, respectively) [16–18]. Consequently, it is likely that haemodynamic depression associated with administration of sodium bicarbonate may be exaggerated during respiratory acidosis. However, there has been no reported *in vivo* investigation examining the detrimental haemodynamic effects of sodium bicarbonate in acid–base derangements. Therefore, the acute haemodynamic effects of sodium bicarbonate solution have been examined during administration into the right atrium in anaesthetized dogs with respiratory or metabolic acidosis and without acidosis.

MATERIALS AND METHODS

Investigations were carried out in 25 adult mongrel dogs of both sexes, weighing 8–13 kg. The study was approved by the Institutional Animal Care and Use Committee. Animals were anaesthetized with i.v. thiamylal 15–20 mg kg^{-1} and the trachea was intubated. The lungs were ventilated mechanically with room air and supplementary oxygen via a cuffed tracheal tube, using a volume-cycled animal ventilator (model R-60, Aika Co., Ltd, Tokyo). End-expiratory concentration of carbon dioxide was monitored continuously using a carbon dioxide analyser (CO_2 Monitor IH31, NEC San-ei Instruments Co., Ltd, Tokyo). Anaesthesia was maintained with 0.7–1.0% halothane inspired in oxygen and air. Suxamethonium 20 mg was given i.v. and thereafter 20 mg h^{-1} was administered i.v. to produce neuromuscular block. During all measurements, pulmonary arterial blood temperature was maintained at 36.5–38.5 °C. Arterial blood was analysed for pH$_a$, Pa_{CO_2}, Pa_{O_2} and base deficit by Acid–Base Laboratory (model ABL 300, Radiometer, Copenhagen), and for

---

TOSHIAKI NISHIKAWA, M.D., Department of Anaesthesiology, Institute of Clinical Medicine, University of Tsukuba, Ibaraki 305, Japan. Present address: Department of Anaesthesiology and Critical Care Medicine, The Johns Hopkins Medical Institutions, Baltimore, MD, U.S.A. Accepted for Publication: September 25, 1992.

Correspondence to Japan.

TABLE I. *Arterial blood-gas and electrolyte values (mean (SEM)) before administration of 0.9% saline and 7% sodium bicarbonate solutions.* *$P < 0.05$, **$P < 0.01$ *compared with two other groups*

	Non-acidosis ($n = 10$)	Respiratory acidosis ($n = 8$)	Metabolic acidosis ($n = 7$)
pH_a	7.39 (0.01)**	7.18 (0.01)**	7.27 (0.01)**
Pa_{CO_2} (kPa)	5.1 (0.1)	10.1 (0.3)**	5.2 (0.1)
Pa_{O_2} (kPa)	16.3 (1.9)	26.0 (4.1)	19.3 (2.8)
Base deficit (mmol litre^{-1})	−1.9 (0.5)	−2.5 (1.1)	−9.0 (0.5)**
Na (mmol litre^{-1})	145 (1)	146 (1)	141 (1)*
K (mmol litre^{-1})	3.6 (0.1)	4.1 (0.2)	3.6 (0.2)
Ca^{2+} (mmol litre^{-1})	1.14 (0.03)	1.16 (0.03)	1.18 (0.01)

blood concentrations of sodium, potassium and ionized calcium (Ca^{2+}) by Analyzer (KNAZ Sodium-Potassium Analyzer, Radiometer, Copenhagen).

An i.v. cannula was placed in a forelimb vein for constant administration of lactated Ringer's solution at a rate of 10 ml kg^{-1} h^{-1}. Lead II of an electrocardiogram (model 2236A, NEC San-ei Instruments Co., Ltd, Tokyo) was monitored with subcutaneous electrodes in the legs. Heart rate was measured continuously on a beat-to-beat basis by a cardiotachometer (model 1321, NEC San-ei Instruments Co., Ltd, Tokyo) triggered by lead II of the electrocardiogram. Arterial pressure measurements and samples for blood-gas analysis were obtained from a femoral arterial catheter. A flow-directed, balloon-tipped pulmonary artery catheter (model 93-132-5F, Baxter Edwards Laboratories, Irvine, California) was inserted via the right external jugular vein for continuous monitoring of pulmonary artery pressure. Another catheter was positioned in the right atrium through a femoral vein to permit continuous measurement of right atrial pressure (RAP). Calibrated Statham P23ID transducers (Gould, Cleveland, Ohio) were used for pressure measurements. A 5-French gauge catheter-tipped transducer (model MPC-500, Millar Instruments Inc., Houston, Texas) was inserted through the left jugular vein and positioned in the right ventricle to obtain right ventricular pressure and instantaneous rate of increase in right ventricular pressure (RV dP/dt) using a differential amplifier (model 1323, NEC San-ei Instruments Co., Ltd, Tokyo).

After the pulmonary trunk was dissected free of the surrounding tissues through a left-sided thoracotomy in the fourth interspace, an electromagnetic flow probe of appropriate size (model FR 10–12 mm, Nihon-Kohden Co., Ltd, Tokyo) was placed carefully around the pulmonary trunk for continuous measurement of pulmonary blood flow (PBF). The flow probe was calibrated with 0.9% saline solution *in vitro* before implantation, and PBF was measured continuously with a square-wave electromagnetic blood flowmeter (model MFV-3200, Nihon-Kohden Co., Ltd, Tokyo). After surgical preparation, all dogs were allowed a stabilization period of at least 60 min. All recordings were made on the eight-channel recorder (model RECTI-HORIZ-8K, NEC San-ei Instruments Co., Ltd, Tokyo) throughout the investigation.

The animals were allocated randomly to three groups: dogs without acidosis ($n = 10$), with respiratory acidosis ($n = 8$) and with metabolic acidosis ($n = 7$). After a period of stabilization in 10 dogs without respiratory (Pa_{CO_2} 4.5–5.6 kPa) and metabolic acidosis (base deficit > -4 mmol litre^{-1}) the haemodynamic effects of 0.9% saline solution 1.2 ml kg^{-1} were observed and recorded continuously for 3 min when administered over 5 s into the right atrium. Subsequently, after another stabilization period of at least 15 min, 7% sodium bicarbonate solution 1 mmol kg^{-1} (1.2 ml kg^{-1}) was injected over 5 s into the right atrium, and haemodynamic changes were recorded continuously for 3 min. Ventilator settings were kept constant during these haemodynamic measurements.

Respiratory acidosis of Pa_{CO_2} 9.1–10.9 kPa was induced by decreasing ventilatory volume in eight dogs, whereas co-existing metabolic acidosis was not corrected. After a period of stabilization, the same haemodynamic measurements were made for 3 min using 0.9% saline solution 1.2 ml kg^{-1} or 7% sodium bicarbonate solution 1 mmol kg^{-1} when these solutions were injected over 5 s into the right atrium.

Metabolic acidosis of base deficit less than −6 mmol litre^{-1} was induced in seven dogs by continuous i.v. infusion of hydrochloric acid 0.2 mol litre^{-1} at an approximate rate of 80–120 ml h^{-1}, while Pa_{CO_2} was maintained at 4.5–5.6 kPa. After stabilization for at least 15 min, haemodynamic measurements were made for 3 min when 0.9% saline solution 1.2 ml kg^{-1} or 7% sodium bicarbonate solution 1 mmol kg^{-1} was injected over 5 s into the right atrium.

All values are expressed as mean (SEM). Both mean arterial pressure (MAP) and mean pulmonary artery pressure (MPAP) were calculated as diastolic pressure plus one-third of the pulse pressure. Analysis of changes in haemodynamic variables from baseline (30 s, 1 and 3 min) and comparisons of data among the three groups (baseline values and maximal changes from baseline) were performed using one-way or two-way analysis of variance (ANOVA), respectively, and Student's t test with Bonferroni correction. Results were considered statistically significant at $P < 0.05$.

RESULTS

Arterial pH was smallest and Pa_{CO_2} greatest in the respiratory acidosis group, whereas base deficit was most pronounced in the metabolic acidosis group. Blood sodium concentration was smallest in the metabolic acidosis group, but within the normal range (table I).

TABLE II. *Haemodynamic responses (mean (SEM)) to a right atrial bolus administration of 0.9% saline solution 1.2 ml kg^{-1}. MAP = mean arterial pressure; HR = heart rate; MPAP = mean pulmonary artery pressure; RAP = right atrial pressure; RV dP/dt = maximal rate of rise of right ventricular pressure; PBF = pulmonary blood flow.* $P < 0.05$: **compared with baseline; †compared with two other groups*

		Time after injection		
	Baseline	30 s	1 min	3 min
Non-acidosis ($n = 10$)				
MAP (mm Hg)	116 (5)	117 (5)	117 (5)	118 (4)
HR (beat min^{-1})	150 (8)	150 (8)	149 (7)	151 (7)
MPAP (mm Hg)	21.4 (2.3)	22.2 (2.9)*	21.9 (2.3)*	21.8 (2.3)
RAP (mm Hg)	3.75 (0.29)	4.15 (0.30)*	4.15 (0.30)*	3.75 (0.29)
RV dP/dt (mm Hg s^{-1})	660 (59)	670 (59)	665 (58)	658 (57)
PBF (ml min^{-1})	1022 (94)	1098 (98)*	1085 (96)*	1045 (93)
Respiratory acidosis ($n = 8$)				
MAP (mm Hg)	103 (6)	101 (7)	102 (6)	100 (6)
HR (beat min^{-1})	140 (10)	143 (10)	142 (9)	142 (9)
MPAP (mm Hg)	24.0 (3.5)	24.7 (3.4)	24.6 (3.5)	24.3 (3.7)
RAP (mm Hg)	6.75 (0.85)†	7.31 (0.93)*	7.13 (0.90)*	7.19 (0.93)*
RV dP/dt (mm Hg s^{-1})	603 (59)	608 (63)	613 (67)	606 (63)
PBF (ml min^{-1})	1012 (170)	1053 (179)	1041 (177)	1031 (187)
Metabolic acidosis ($n = 7$)				
MAP (mm Hg)	97 (4)	98 (5)	99 (5)	99 (5)
HR (beat min^{-1})	134 (6)	135 (6)	135 (6)	134 (6)
MPAP (mm Hg)	17.4 (1.0)	18.5 (1.1)*	18.3 (1.1)*	18.0 (1.1)
RAP (mm Hg)	3.28 (0.37)	3.64 (0.37)*	3.57 (0.40)	3.43 (0.35)
RV dP/dt (mm Hg s^{-1})	646 (61)	657 (64)	661 (64)	657 (65)
PBF (ml min^{-1})	1100 (109)	1168 (114)*	1168 (114)*	1143 (114)

TABLE III. *Haemodynamic responses (mean (SEM)) to a right atrial bolus administration of 7% sodium bicarbonate 1 mmol kg^{-1} (1.2 ml kg^{-1}).* $P < 0.05$: **compared with baseline; †compared with two other groups; §compared with non-acidosis group*

		Time after injection		
	Baseline	30 s	1 min	3 min
Non-acidosis ($n = 10$)				
MAP (mm Hg)	117 (5)	101 (5)*	116 (5)	120 (4)
HR (beat min^{-1})	151 (7)	149 (7)	150 (7)	151 (8)
MPAP (mm Hg)	21.4 (2.3)	20.7 (2.1)	22.5 (2.2)*	22.7 (2.4)*
RAP (mm Hg)	3.80 (0.33)	5.60 (0.43)*	5.15 (0.40)*	4.40 (0.28)*
RV dP/dt (mm Hg s^{-1})	640 (63)	540 (48)*	660 (60)	695 (69)*
PBF (ml min^{-1})	1036 (92)	1045 (105)	1158 (97)*	1195 (99)*
Respiratory acidosis ($n = 8$)				
MAP (mm Hg)	99 (6)	80 (8)*	87 (13)	98 (11)
HR (beat min^{-1})	142 (9)	145 (9)	149 (9)	141 (8)
MPAP (mm Hg)	24.8 (3.7)	21.0 (3.0)	22.8 (3.6)	24.9 (3.9)
RAP (mm Hg)	7.75 (0.75)†	10.2 (0.98)*	9.94 (1.11)*	9.50 (1.56)
RV dP/dt (mm Hg s^{-1})	617 (73)	419 (65)*	514 (91)	572 (100)
PBF (ml min^{-1})	963 (170)	700 (148)*	850 (217)	959 (234)
Metabolic acidosis ($n = 7$)				
MAP (mm Hg)	99 (5)§	87 (6)	100 (6)	104 (4)
HR (beat min^{-1})	135 (7)	131 (6)	134 (5)	136 (6)
MPAP (mm Hg)	17.9 (1.2)	17.2 (1.3)	18.6 (1.2)	19.0 (1.4)*
RAP (mm Hg)	3.28 (0.37)	5.14 (0.57)*	4.43 (0.42)*	3.79 (0.37)*
RV dP/dt (mm Hg s^{-1})	657 (60)	536 (72)*	639 (75)	707 (67)*
PBF (ml min^{-1})	1121 (122)	1139 (83)	1211 (103)	1275 (128)*

Baseline RAP before administration of 0.9% saline solution was significantly greater in respiratory acidosis compared with the two other groups ($P < 0.05$) (table II). Administration of 0.9% saline solution 1.2 ml kg^{-1} into the right atrium over 5 s caused small but significant increases in RAP in all three groups, and significant increases in MPAP and PBF in the metabolic acidosis and non-acidosis groups.

Before administration of sodium bicarbonate, baseline RAP was greater in the respiratory acidosis group compared with the two other groups ($P < 0.05$) (table III). Both acidosis groups had decreased baseline MAP values; in the metabolic acidosis group, the difference just reached significance compared with the non-acidosis group ($P < 0.05$).

The most frequently observed haemodynamic changes after administration of sodium bicarbonate included transient decreases in MAP and RV d*P*/d*t*, and increased RAP, followed by gradual return to baseline values, or greater. No significant changes in HR were observed in all groups. However, PBF responses to a 5-s administration of sodium bi-

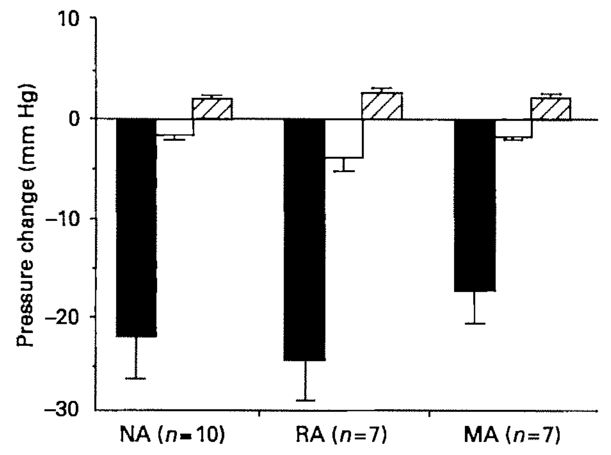


FIG. 1. Maximal changes (mean, SEM) in mean arterial pressure (MAP) (■), mean pulmonary artery pressure (MPAP) (□) and right atrial pressure (RAP) (▨) from baseline values within 1 min after the administration of sodium bicarbonate 1 mmol kg^{-1} into the right atrium in dogs with no acidosis (NA), respiratory acidosis (RA) and metabolic acidosis (MA). The mean (SEM) times at which maximal changes of MAP, MPAP and RAP occurred after the administration of sodium bicarbonate were: MAP—25 (3) s, 34 (5) s, 24 (4) s; MPAP—20 (1) s, 27 (3) s, 17 (3) s; RAP—24 (3) s, 23 (5) s, 21 (3) s in non-acidosis, respiratory acidosis and metabolic acidosis groups, respectively. There were no significant differences in these haemodynamic variables among the three groups.

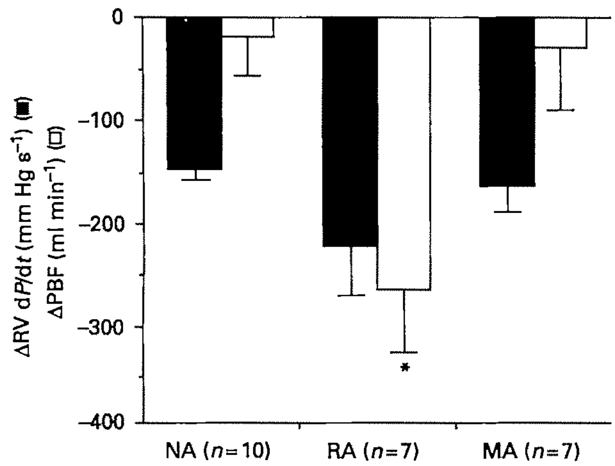


FIG. 2. Maximal changes (mean, SEM) in right ventricular dP/dt (RV dP/dt) (■) and pulmonary blood flow (PBF) (□) from baseline values within 1 min after the administration of sodium bicarbonate 1 mmol kg^{-1} into the right atrium in dogs with no acidosis (NA), respiratory acidosis (RA) and metabolic acidosis (MA). The mean (SEM) times at which maximal changes of RV dP/dt and PBF occurred after the administration of sodium bicarbonate were: RV dP/dt—19 (2) s, 23 (3) s, 21 (1) s; PBF—24 (2) s, 30 (2) s, 24 (2) s in non-acidosis, respiratory acidosis and metabolic acidosis groups, respectively. $^*P < 0.05$ compared with non-acidosis and metabolic acidosis groups.

carbonate were not consistent among the three groups (table III); a profound reduction of PBF occurred immediately after injection of sodium bicarbonate in the respiratory acidosis group.

In one of the eight dogs with respiratory acidosis, progressive circulatory depression and cardiac arrest occurred 6 min after the injection of sodium bicarbonate; the data of this dog were excluded from figures 1 and 2, which show maximal changes in haemodynamic values within 1 min after injection of sodium bicarbonate. Although MAP, MPAP and RAP of the three groups showed comparable alterations from baseline values after administration of sodium bicarbonate (fig. 1), there was a significant reduction in PBF in the respiratory acidosis group compared with those in the two other groups ($P < 0.05$) (fig. 2).

DISCUSSION

This study has shown that the haemodynamic depression after administration of 7% sodium bicarbonate 1 mmol kg^{-1} into the right atrium over a period of 5 s was augmented by respiratory acidosis. As the haemodynamic alterations associated with sodium bicarbonate were smaller in dogs without respiratory acidosis, the considerable haemodynamic deterioration after sodium bicarbonate in dogs with respiratory acidosis could be attributed to a decreased $\mathrm{pH_a}$ before bicarbonate administration, further reduction of intracellular pH caused by diffusion of carbon dioxide into the myocardial cells or both. The results suggest that, if severe respiratory acidosis exists, sodium bicarbonate should be given cautiously to correct metabolic acidosis.

Although there are conflicting data [12–15, 19, 20] on the major determinants of myocardial performance during acid–base disturbances (intra- or extracellular pH, $P\mathrm{CO_2}$ and bicarbonate), $P\mathrm{CO_2}$ or intracellular pH appears to be more important. In an animal study [15] of simultaneous changes in intracellular and extracellular pH during acidosis, at the same extracellular pH, it was shown that respiratory acidosis caused greater depression in myocardial contractility and greater intracellular acidosis of the heart than metabolic acidosis. In addition, intracellular acidosis may be aggravated by administration of sodium bicarbonate ("paradoxical" acidosis) [4, 21], because of free diffusion of carbon dioxide, generated by bicarbonate, into the cells. In the present study, extracellular pH in the respiratory acidosis group was 7.18 (table I) and intracellular pH may have decreased to less than 7.00 [21]. This may account for the observation that haemodynamic depression was most marked (table II, fig. 2) and there was a cardiac arrest in the respiratory acidosis group. However, a further study should be undertaken to evaluate the haemodynamic effect of sodium bicarbonate during respiratory and metabolic acidosis at the same arterial pH, as the $\mathrm{pH_a}$ was significantly greater in the metabolic acidosis group than in the respiratory acidosis group in the present study, and may have contributed in part to the lesser haemodynamic depression after sodium bicarbonate during metabolic acidosis.

The depressant effect of carbon dioxide on myocardial contractility seems to be evident when the $\mathrm{pH_a}$ decreases to less than 7.00 during respiratory acidosis [22–24]. Hypercapnia is accompanied by systemic peripheral vasoconstriction [22]. However, there are also conflicting data showing increased cardiac output associated with systemic vasodilatation during respiratory acidosis [25]. This discrepancy may be attributed to different anaesthetic agents used and the stimulant effect of carbon dioxide on the sympathoadrenal system, which can compensate for the direct cardiovascular depressant effect of carbon dioxide. It is likely, therefore, that the significant increase in RAP observed in the respiratory acidosis group (tables II, III) was caused by peripheral vasoconstriction secondary to hypercapnia.

The dose of sodium bicarbonate used in the present study was based on the standards for cardiopulmonary resuscitation [3] and previous reports [7, 9]. The injection rate of sodium bicarbonate is likely to affect the degree of associated haemodynamic alterations to as great an extent as the total dose. However, there is no "standard" rate of sodium bicarbonate administration in cardiopulmonary resuscitation [3]. The 5-s period of administration of sodium bicarbonate was chosen according to previous experimental reports in which sodium bicarbonate approximately 1 mmol kg^{-1} was given as a bolus injection or over 5–15 s [1, 2, 7, 9].

In conclusion, this experiment suggests that haemodynamic depression after the i.v. administration of sodium bicarbonate is pronounced during respiratory acidosis. If severe respiratory acidosis exists, bicarbonate should be administered cautiously for the correction of metabolic acidosis.

ACKNOWLEDGEMENT

This experiment was supported by University of Tsukuba Project Research. The author thanks Ms Y. Isaka for her help in conducting the study.

REFERENCES

1. Redding JS, Pearson JW. Resuscitation from ventricular fibrillation. *Journal of American Medical Association* 1968; **203**: 255–260.
2. Minuck M, Sharma GP. Comparison of THAM and sodium bicarbonate in resuscitation of the heart after ventricular fibrillation in dogs. *Anesthesia and Analgesia* 1977; **56**: 38–45.
3. Standards and guidelines for cardiopulmonary resuscitation (CPR) and emergency cardiac care (ECC). *Journal of American Medical Association* 1986; **255**: 2942.
4. Arieff AI, Leach W, Park R, Lazarowitz VC. Systemic effects of $NaHCO_3$ in experimental lactic acidosis in dogs. *American Journal of Physiology* 1982; **242**: F586–591.
5. Arieff AI. Indications for use of bicarbonate in patients with metabolic acidosis. *British Journal of Anaesthesia* 1991; **67**: 165–177.
6. Graf H, Leach W, Arieff AI. Evidence for a detrimental effect of bicarbonate therapy in hypoxic lactic acidosis. *Science* 1985; **227**: 754–756.
7. Guerci AD, Chandra N, Johnson E, Rayburn B, Wurmb E, Tsitlik J, Halperin HR, Siu C, Weisfeldt ML. Failure of sodium bicarbonate to improve resuscitation from ventricular fibrillation in dogs. *Circulation* 1986; **74**: (Suppl. IV): 75–79.
8. von Planta M, Weil MH, Gazmuri RJ, Bisera J, Rackow EC. Myocardial acidosis associated with CO_2 production during cardiac arrest and resuscitation. *Circulation* 1989; **80**: 684–692.
9. Huseby JS, Gumprecht DG. Hemodynamic effects of rapid bolus hypertonic sodium bicarbonate. *Chest* 1981; **79**: 552–554.
10. Cooper DJ, Worthley LIG. Adverse haemodynamic effects of sodium bicarbonate in metabolic acidosis. *Intensive Care Medicine* 1987; **13**: 425–427.
11. Bersin RM, Chatterjee K, Arieff AI. Metabolic and hemodynamic consequences of sodium bicarbonate administration in patients with heart disease. *American Journal of Medicine* 1989; **87**: 7–14.
12. Clancy RL, Cingolani HE, Taylor RR, Graham TP jr, Gilmore JP. Influence of sodium bicarbonate on myocardial performance. *American Journal of Physiology* 1967; **212**: 917–923.
13. McElroy WT jr, Gerdes AJ, Brown EB jr. Effects of CO_2, bicarbonate and pH on the performance of isolated perfused guinea pig hearts. *American Journal of Physiology* 1958; **195**: 412–426.
14. Cingolani HE, Mattiazzi AR, Blesa ES, Gonzalez NC. Contractility in isolated mammalian heart muscle after acid–base changes. *Circulation Research* 1970; **26**: 269–278.
15. Steenbergen C, Deleeuw G, Rich T, Williamson JR. Effects of acidosis and ischemia on contractility and intracellular pH of rat heart. *Circulation Research* 1977; **41**: 849–858.
16. Martin GB, Carden DL, Nowak RM, Tomlanovich MC. Comparison of central venous and arterial pH and $P\text{CO}_2$ during open-chest CPR in the canine model. *Annals of Emergency Medicine* 1985; **14**: 529–533.
17. Weil MH, Rackow EC, Trevino R, Grundler W, Falk JL, Griffel MI. Difference in acid–base state between venous and arterial blood during cardiopulmonary resuscitation. *New England Journal of Medicine* 1986; **315**: 153–156.
18. Adrogué HJ, Rashad MN, Gorin AB, Yacoub J, Madias NE. Assessing acid–base status in circulatory failure. Differences between arterial and central venous blood. *New England Journal of Medicine* 1989; **320**: 1312–1316.
19. Ng ML, Levy MN, Zieske HA. Effects of changes of pH and of carbon dioxide tension on left ventricular performance. *American Journal of Physiology* 1967; **213**: 115–120.
20. Cingolani HE, Faulkner SL, Mattiazzi AR, Bender HW, Graham TP jr. Depression of human myocardial contractility with "respiratory" and "metabolic" acidosis. *Surgery* 1975; **77**: 427–432.
21. Shapiro JI, Whalen M, Kucera R, Kindig N, Filley G, Chan L. Brain pH responses to sodium bicarbonate and Carbicarb during systemic acidosis. *American Journal of Physiology* 1989; **256**: H1316–1321.
22. Caress DL, Kissack AS, Slovin AJ, Stuckey JH. The effect of respiratory and metabolic acidosis on myocardial contractility. *Journal of Thoracic and Cardiovascular Surgery* 1968; **56**: 571–577.
23. Boniface KJ, Brown JM. Effect of carbon dioxide excess on contractile force of heart, *in situ*. *American Journal of Physiology* 1953; **172**: 752–756.
24. Monroe RG, French G, Whittenberger JL. Effects of hypocapnia and hypercapnia on myocardial contractility. *American Journal of Physiology* 1960; **199**: 1121–1124.
25. Andersen MN, Mouritzen C. Effect of acute respiratory and metabolic acidosis on cardiac output and peripheral resistance. *Annals of Surgery* 1966; **163**: 161–168.

British Journal of Anaesthesia 1993; 70: 201–204

PLASMA CONCENTRATIONS OF BUPIVACAINE AND ITS ENANTIOMERS DURING CONTINUOUS EXTRAPLEURAL INTERCOSTAL NERVE BLOCK

R. G. BERRISFORD, S. SABANATHAN, A. J. MEARNS, B. J. CLARKE AND A. HAMDI

SUMMARY

Plasma concentrations of bupivacaine have been measured in 12 patients given bupivacaine through a paravertebral catheter placed under direct vision at thoracotomy. After an initial bolus of 0.5% bupivacaine 20 ml, mean (SEM) $C_P$max was 1.45 (0.32) $\mu g\ ml^{-1}$ and median (range) t$C_P$max was 25 (10–60) min. A concentration of 4.43 $\mu g\ ml^{-1}$ measured in one patient was not associated with toxic signs. During continuous infusion of bupivacaine for 120 h, $C_P$max was 4.9 (0.7) $\mu g\ ml^{-1}$ and t$C_P$max 48 (5–96) h. No symptoms or signs of toxicity occurred. Separate measurement of R- and S-bupivacaine concentrations demonstrated significantly different concentration–time profiles. (Br. J. Anaesth. 1993; **70**: 201–204)

KEY WORDS

Anaesthetics, local: bupivacaine. Anaesthetic techniques, regional: paravertebral block. Pharmacokinetics: bupivacaine infusions. Toxicity.

Continuous extrapleural intercostal nerve block is an effective method of analgesia for patients undergoing thoracotomy [1]. It has been shown to reduce pain scores, minimize reduction in lung volumes [2] and reduce the incidence of pulmonary complications after lung resection [3]. While the rate at which bupivacaine is infused does not exceed the maximum recommended dose (2 $mg\ kg^{-1}/4\ h$), there remains the potential for bupivacaine toxicity.

Bupivacaine is a synthetic chiral compound comprising two optically active enantiomers, R-bupivacaine and S-bupivacaine. It is administered as a racemic mixture of these two enantiomers (RS-bupivacaine). As enantiomers may differ in their pharmacokinetics, pharmacological effects and toxicity, full evaluation of the potential toxicity of bupivacaine requires separate measurement of R- and S-enantiomers [4–6].

This study was undertaken to measure plasma bupivacaine concentrations achieved during continuous extrapleural intercostal nerve block.

PATIENTS AND METHODS

The study was approved by the local Ethics Committee and all patients gave informed consent. Twelve consecutive patients (ASA I) undergoing thoracotomy for anti-reflux procedures were investigated. Patients were excluded if they received a peroperative blood transfusion, lost more than 1 litre of blood, or were taking histamine antagonists which may affect bupivacaine metabolism [7]. Hepatic and renal disease was excluded on the basis of preoperative blood tests.

All patients received a sleep dose of thiopentone, vecuronium 0.1 $mg\ kg^{-1}$ and phenoperidine (1 mg if weight less than 50 kg, 2 mg if weight greater than 50 kg). Intermittent positive pressure ventilation was used with 66% nitrous oxide in oxygen supplemented with 0–1% isoflurane or 0–1.5% enflurane. Mean end-tidal carbon dioxide concentration was maintained at 4–5% and pulse oximetry saturation greater than 90%.

Towards the end of the operation, a 16-gauge extradural catheter was placed against the paravertebral space after the posterior parietal pleura had been raised as described previously [1, 2]. The tip of the catheter was inserted into the paravertebral space through a defect made in the extrapleural fascia [8].

A bolus of 0.5% plain bupivacaine 20 ml was given through the catheter when it had been secured in place ($t = 0$). The continuous infusion of bupivacaine was started 1 h later ($t = 60$ min). To remain within the guideline dosage of 2 $mg\ kg^{-1}/4\ h$, the rate of infusion was set according to body weight and continued until the morning of the fifth day after operation: 50–59 kg—5 $ml\ h^{-1}$ (25 $\mu g\ h^{-1}$); 60–69 kg—6 $ml\ h^{-1}$ (30 $\mu g\ h^{-1}$); 70–79 kg—7 $ml\ h^{-1}$ (35 $\mu g\ h^{-1}$); 80–89 kg—8 $ml\ h^{-1}$ (40 $\mu g\ h^{-1}$); 90–99 kg—9 $ml\ h^{-1}$ (45 $\mu g\ h^{-1}$); more than 100 kg—10 $ml\ h^{-1}$ (50 $\mu g\ h^{-1}$).

Blood samples were collected from a central venous catheter into pre-cooled polypropylene tubes, centrifuged and stored at −20 °C until required for analysis. Samples were collected at 10, 20, 30, 45 and 60 min after initial bolus injection, 5, 20, 60, 120, 180, 240, 360 and 480 min after the infusion began and at 24, 48, 72, 96 and 120 h after operation.

R. G. BERRISFORD, B.SC., F.R.C.S.; S. SABANATHAN, M.D., F.R.C.S., F.I.C.A.; A. J. MEARNS, F.R.C.S.; Department of Thoracic Surgery, Bradford Royal Infirmary, Duckworth Lane, Bradford BD9 6RJ. B. J. CLARKE, M.SC., PH.D.; A. HAMDI, PH.D.; Department of Pharmaceutical Chemistry, School of Pharmacy, University of Bradford, Bradford BD7 1DP. Accepted for Publication: July 7, 1992.

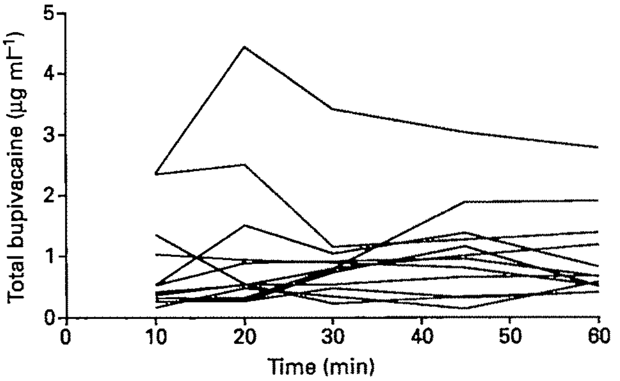


FIG. 1. Plasma bupivacaine concentrations from 12 individual patients after bolus paravertebral injection of 0.5 % bupivacaine.

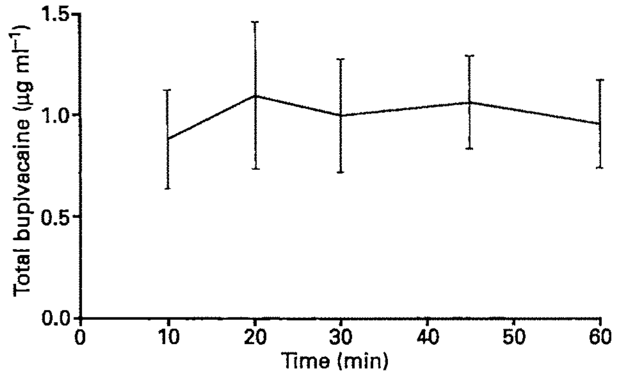


FIG. 2. Mean (SEM) plasma bupivacaine concentrations after bolus paravertebral injection of 0.5 % bupivacaine.

TABLE I. *Maximum bupivacaine concentrations after bolus paravertebral injection of 0.5 % bupivacaine 20 ml*

Patient No.	$C_P$max (µg ml^{-1})	tC_Pmax (min)
1	2.50	20
2	0.63	45
3	1.50	20
4	4.43	20
5	0.47	20
6	1.03	10
7	1.35	10
8	1.13	45
9	0.46	30
10	0.93	45
11	1.14	60
12	1.86	45
Mean (SEM)	1.45 (0.32)	—
Median (range)	—	25 (10–60)

Plasma concentrations of bupivacaine were measured by high pressure liquid chromatography (HPLC). Total bupivacaine with its R- and S-enantiomers were measured by a coupled chiral–achiral HPLC method [9].

Maximum plasma concentration of bupivacaine ($C_P$max) and the time it was attained (tC_Pmax) during initial bolus and during continuous infusion were recorded.

Analysis of variance was used to determine the significance of differences between concentrations of RS-, R- and S-bupivacaine.

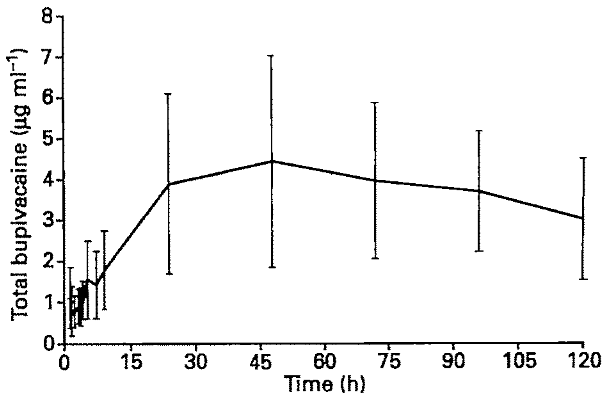


FIG. 3. Mean (SEM) plasma bupivacaine concentrations (racemic) after continuous paravertebral infusion. Time zero represents 60 min after bolus injection.

RESULTS

Patient characteristics were: age range 27–64 yr, mean (SEM) weight 75.2 (3.9) kg, sex ratio 6:6. No patient reported symptoms of bupivacaine toxicity, neither were any signs of toxicity observed.

Bupivacaine assay

For the concentration range 1–20 µg ml^{-1} of aqueous standards, the regression equation was $y = 8.14x + 1.06$ ($r = 0.999$, $n = 12$). Repeatability for a standard at 10 µg ml^{-1} was 0.58 % ($n = 8$). The limit of detection for bupivacaine in pooled serum was 13 ng on column for a 50-µl injection [9].

Bupivacaine concentrations after bolus injection

RS-Bupivacaine concentrations measured during the first 60 min after injection are shown for individual patients in figure 1; mean values are shown in figure 2. Values for $C_P$max are shown in table I. One patient exhibited greater concentrations compared with the remainder, although they were not associated with symptoms or signs of toxicity. Mean (SEM) $C_P$max was 1.45 (0.32) µg ml^{-1} and median tC_Pmax 25 min (range 10–60 min), although there was wide variation between individual patients.

Bupivacaine concentrations during infusion

After the initial peak after the bolus injection, there was a gradual increase to a mean (SEM) peak RS-bupivacaine concentration of 4.92 (0.7) µg ml^{-1} at 48 (5–96) h (fig. 3, table II). Subsequent concentrations were smaller, although this decrease was not significant. The greatest concentration of RS-bupivacaine measured in any patient was 7.48 µg ml^{-1}. However, there were no symptoms or signs of bupivacaine toxicity.

Plasma concentrations of R- and S-bupivacaine are shown in figure 4. Concentrations differed significantly at 30, 45, 210, 300 and 420 min and at 24, 48 and 96 h.

DISCUSSION

There is an extensive literature on plasma bupivacaine concentrations after injection for regional anaesthetic techniques [10]. However, to our knowl-

TABLE II. *Maximum bupivacaine concentrations after continuous paravertebral infusion of 0.5% bupivacaine (dose according to body weight)*

Patient No.	$C_P$max (μg ml^{-1})	tC_Pmax (min)
1	4.90	48
2	1.70	5
3	9.27	48
4	5.26	72
5	5.75	48
6	7.48	48
7	1.29	96
8	3.35	72
9	5.32	72
10	7.38	24
11	4.96	72
12	2.44	24
Mean (SEM)	4.92	—
Median (range)	—	48 (5–96)

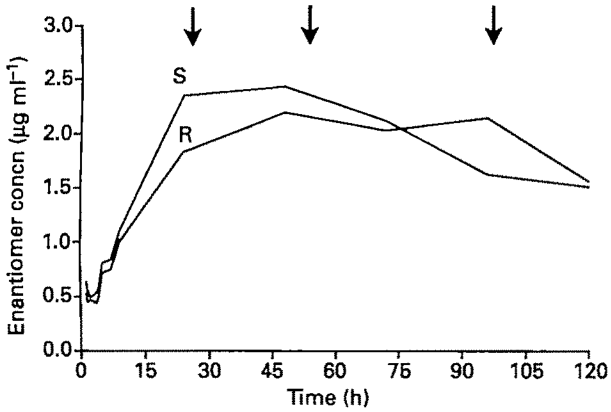


FIG. 4. Plasma R- and S-bupivacaine concentrations during continuous paravertebral infusion of RS-bupivacaine. Although mean concentration appeared different at times (arrows), differences were not statistically significant.

edge, bupivacaine concentrations attained during bolus and continuous paravertebral infusion have not been documented before.

After bolus paravertebral injection, mean $C_P$max (1.45 μg ml^{-1}) was less than the presumed toxic plasma concentration. Smaller concentrations have been measured when other regional techniques have been used for post-thoracotomy analgesia [11]. Median tC_Pmax (25 min) was similar to tC_Pmax measured after other techniques. For comparison, tC_Pmax after intercostal injection was 10–20 min, after extradural injection 15–30 min [12] and after interpleural injection, 20 min [13].

Systemic accumulation of bupivacaine seen in this study during continuous paravertebral infusion occurs also after continuous infusion via other routes. Increasing concentrations, in some cases greater than 4 μg ml^{-1}, have been measured after 48 h of extradural infusion [14]. After continuous interpleural infusion, mean venous concentrations of bupivacaine 2.29 μg ml^{-1} (range 0.72–4.24 μg ml^{-1}) at 48 h [10] and 4.25 μg ml^{-1} and 2.5 μg ml^{-1} at 24 h [15] have been measured. None of these authors reported associated toxicity. We are not aware of any study which has documented bupivacaine concentrations after 120 h of infusion by any route.

Systemic accumulation may be explained in terms of plasma protein binding. Bupivacaine is 92% bound to plasma proteins in man (at 1.0 μg ml^{-1}) [16] and only free drug concentration determines biological action and therefore toxicity. Thus total drug concentration measured in most studies does not reflect active (potentially toxic) drug concentrations. A marked increase in plasma alpha$_1$ acid glycoprotein occurs after surgery and is associated with increased plasma drug binding [17]. Therefore, although total drug concentration may exceed "minimal toxic concentration", free drug concentration may remain within acceptable limits after operation [18]. This has been confirmed by a study in patients undergoing cholecystectomy given i.v. bupivacaine; total plasma drug concentrations doubled after operation, whilst unbound (active) drug concentrations were similar to those measured before operation [19].

REFERENCES

1. Sabanathan S, Bickford-Smith PJ, Pradhan GN, Hashimi H, Eng JB, Mearns AJ. Continuous intercostal nerve block for pain relief after thoracotomy. *Annals of Thoracic Surgery* 1988; **46**: 425–426.
2. Sabanathan S, Mearns AJ, Bickford-Smith PJ, Eng J, Berrisford RG, Bibby SR, Majid MR. Efficacy of continuous extrapleural intercostal nerve block on postthoracotomy pain and pulmonary mechanics. *British Journal of Surgery* 1990; **77**: 221–225.
3. Berrisford RG, Sabanathan S, Mearns AJ, Bickford-Smith PJ. Pulmonary complications after lung resection; the effect of continuous extrapleural intercostal nerve block. *European Journal of Cardiothoracic Surgery* 1990; **4**: 407–410.
4. Tucker GT, Lennard MS. Enantiomer specific pharmacokinetics. *Pharmaceutical Therapeutics* 1990; **45**: 309–329.
5. Mather LE. Disposition of mepivacaine and bupivacaine enantiomers in sheep. *British Journal of Anaesthesia* 1991; **67**: 239–246.
6. Lee EJ, Ang SB, Lee TL. Stereoselective high-performance liquid chromatographic assay for bupivacaine enantiomers. *Journal of Chromatography* 1987; **420**: 203–206.
7. Noble DW, Smith KJ, Dundas CR. Effects of H-2 antagonists on the elimination of bupivacaine. *British Journal of Anaesthesia* 1987; **59**: 735–737.
8. Berrisford RG, Sabanathan S. Direct access to the paravertebral space at thoracotomy. *Annals of Thoracic Surgery* 1990; **49**: 509–510.
9. Clark BJ, Hamdi A, Berrisford RG, Sabanathan S, Mearns AJ. Reversed-phase and high-performance liquid chromatographic assay of bupivacaine and its enantiomers after continuous extrapleural infusion. *Journal of Chromatography* 1991; **553**: 383–390.
10. Rosenburg PH, Scheinen BM-A, Lepantalo MJA, Lindfors O. Continuous intrapleural infusion of bupivacaine for analgesia after thoracotomy. *Anesthesiology* 1987; **67**: 811–813.
11. Ferrante FM, Chan VWS, Arthur GR, Rocco AG. Interpleural analgesia after thoracotomy. *Anesthesia and Analgesia* 1991; 72: 105–109.
12. Moore DC, Mather LE, Bridenbaugh PO, Bridenbaugh LD, Balfour RL, Lysons DF, Horton WG. Arterial and venous plasma levels of bupivacaine following epidural and intercostal nerve blocks. *Anesthesiology* 1976; **45**: 39–45.
13. Reiestad F, Strokskag KE, Holmquist E. Intrapleural administration of bupivacaine in postoperative management of pain. *Anesthesiology* 1986; **65**: A205.
14. Ross RA, Clarke JE, Armitage EN. Postoperative pain prevention by continuous epidural infusion. *Anaesthesia* 1980; **35**: 663.
15. McIlvaine WB, Knox RF, Jones M, Bloedow D, Fennessey P, Goldstein M. Continuous infusion of bupivacaine via intrapleural catheter for analgesia after thoracotomy in children. *Regional Anaesthesia* 1987; **12**: 25–26.

16. Mather LE, Long GJ, Thomas J. The intravenous toxicity and clearance of bupivacaine in man. *Clinical Pharmacology and Therapeutics* 1971; **12**: 935–943.
17. Rem J, Saxtrup-Nielson O, Brandt MR, Kehlet H. Influence of epidural analgesia on postoperative changes in various acute phase proteins. *Abstracts 7th World Congress in Anaesthesia, Hamburg*. Amsterdam, Oxford, Princeton: Exerpta Medica, 1980; 374.
18. Tucker GT. Pharmacokinetics of local anaesthetics. *British Journal of Anaesthesia* 1986; **58**: 717–731.
19. Hasselstrom L, Nortved-Sorensen J, Kehlet H, Juel-Christiansen N, Brynjolff I, Munck O, Tucker GT. The influence of systemically administered bupivacaine on cardiovascular function in cholecystectomised patients. *Acta Anaesthesiologica Scandinavica* 1985; **29** (Suppl. 80): 76.

British Journal of Anaesthesia 1993; **70**: 205–213

REVIEW ARTICLE

THE HAEMOSTATIC RESPONSE TO SURGERY AND TRAUMA

W. G. MURPHY, M. J. DAVIES AND A. EDUARDO

Perceptions of the physiological mechanisms of coagulation are undergoing substantial changes. For example, the classical divide of coagulation cascades into intrinsic and extrinsic systems is not relevant to humans: no coagulopathy, or indeed disease state, is associated with deficiencies of several of the proteins of the intrinsic system. The cascade of thrombin generation is via tissue factor, factor VII and factors IX and X, with an absolute requirement for platelet phospholipid matrix and factors VIII:C and V as cofactors (fig. 1). Perhaps of greater importance in practical understanding of the complex acquired coagulopathies such as disseminated intravascular coagulation (DIC) or those following cardiopulmonary bypass surgery or massive resuscitation is that seemingly subtle changes, not measured easily by current coagulation tests, may be far more important than the changes measured by those tests. For example, inability of platelets to stick at sites of injury may be a more limiting factor in haemostasis than the concentrations of circulating soluble coagulation factors. The recent demonstration that large doses of the protease inhibitor, aprotinin, almost completely abolish the acquired coagulopathy of cardiopulmonary bypass surgery (and improve haemostasis in other surgical states) has taken the haemostasis world by surprise; the discovery was serendipitous and the mechanism is still speculative. Attention is now focused on the action of proteases on the platelet surface. What is clear is that there has been a fundamental gap in our understanding of the genesis of coagulopathy in cardiopulmonary bypass; this gap persists, and may also be involved in the understanding of other acquired coagulopathies.

THE PHYSIOLOGY OF COAGULATION: AN OVERVIEW

After vessel rupture, several sequential events occur that attempt to plug the hole. Obviously, physiological coagulation cannot stop large volume flow through a severed vessel (although "surgical" bleeding may be overdiagnosed [77]: a poor clot may disintegrate rapidly, allowing what would otherwise have been a securely haemostatic vessel to rebleed).

The starting point is that the soluble protein, von Willebrand factor, must attach to the exposed subendothelium in the damaged vessel. Failure here results in failure to achieve haemostasis. Absence of von Willebrand factor (von Willebrand's disease), or rarely, absence or malfunction of collagen (as may arise in scurvy) in the subendothelium, prevents this first step taking place.

If von Willebrand factor has bound, and if that von Willebrand factor is structurally normal, then the next step can proceed. Some details of this step remain to be clarified, but essentially the subendothelium-bound von Willebrand factor now exposes multiple intrinsic binding sites for a specific platelet membrane structure termed GPIb. This glycoprotein is fully functional on the resting circulating platelet. *It is likely that this von Willebrand factor–GPIb binding is of critical importance in the complex surgical coagulopathies*, and it is possible that manipulation of this event is a prime site of action of aprotinin.

This step fails if:

(a) There are too few platelets. Haemostasis may be impaired when the circulating platelet count de-

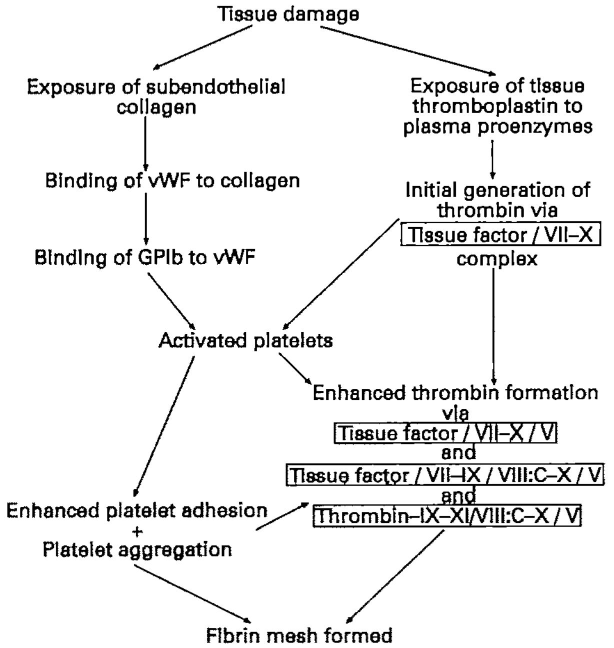

Tissue damage
Exposure of subendothelial collagen
Exposure of tissue thromboplastin to plasma proenzymes
Binding of vWF to collagen
Initial generation of thrombin via
Tissue factor / VII–X
complex
Binding of GPIb to vWF
Activated platelets
Enhanced thrombin formation via
Tissue factor / VII–X / V
and
Tissue factor / VII–IX / VIII:C–X / V
and
Thrombin–IX–XI/VIII:C–X / V
Enhanced platelet adhesion
+
Platelet aggregation
Fibrin mesh formed

FIG. 1. Coagulation cascade. vWF = von Willebrand factor; GPIb = glycoprotein GPIb.

(Br. J. Anaesth. 1993; **70**: 205–213)

KEY WORDS
Blood: coagulation.

W. G. MURPHY, M.D., M.R.C.P., M.R.P.C.PATH.; M. J. DAVIES, F.R.C.S.; A. EDUARDO, M.D.; Edinburgh & South East Scotland Blood Transfusion Service, Royal Infirmary, Lauriston Place, Edinburgh EH3 9HB.
Correspondence to W.G.M.

creases to less than 100×10^9 litre^{-1}. At a circulating count of less than 50×10^9 litre^{-1}, a critical impairment of haemostatic response to surgery or trauma can be anticipated and spontaneous bleeding may occasionally occur [13].

(b) The platelets are not delivered to the periphery of the flowing blood. Platelets in arterial and arteriolar blood are not distributed evenly across the column of blood, but are concentrated in the peripheral areas, while the red cells preferentially flow in the central area. These flow characteristics are not maintained when the PCV decreases to less than 20%, with a result that there is a functional dilution of platelets within the blood stream [21], which may impair haemostasis.

(c) The platelets lack the GPIb receptor. This condition may arise during cardiopulmonary bypass, from proteolytic degradation of the receptor [65]. It is a feature of platelets for transfusion that have been stored for 3 days or longer [8, 10, 26]. It also arises in the rare congenital Bernard–Soulier syndrome.

(d) The GPIb receptor is already occupied, or is otherwise functionally inert. Failure of initial platelet adhesion may contribute to coagulopathy in myeloma, in some cases of idiopathic thrombocytopenic purpura [18], and after infusion of Dextran [1].

Failure of the GPIb–von Willebrand factor axis results in total haemostatic failure—the next two steps of haemostasis (the generation of a platelet plug and the solidification of that plug by fibrin) are completely dependent on platelets adhering at the site of injury.

The only practicable test of this axis in acute clinical situations is the bleeding time; other tests such as the platelet count and the prothrombin or partial thromboplastin times do not reflect the status of this essential axis. The bleeding time has poor predictive value as a *screening* test in the general population; however, in a patient with a clinically manifest coagulopathy it is a useful indicator of impairment of this part of platelet function [47].

The platelet that adheres at a site of injury is exposed to several activating stimuli and to concentrations of adhesive proteins, that enhance the initial adhesion and that allow other platelets to accrete on those already attached. Activation of platelets by thrombin, ADP and perhaps by von Willebrand factor–GPIb binding itself [44] progresses through several metabolic pathways [45] to induce spreading of the platelets over the damaged surface. Secretion of several procoagulant and ligand proteins from the alpha and dense granules of the platelet occurs, together with exposure of other binding sites on the platelet surface, important among which are glycoprotein IIbIIIa, which binds von Willebrand factor and fibrinogen under physiological conditions [34, 75], and the phospholipid, phosphatidylserine, which serves as the essential surface upon which the next step takes place.

Platelets will not form a satisfactory platelet plug or a base for subsequent fibrin formation if they are too few, or functionally inept. Prior activation, such as may occur in cardiopulmonary bypass, *ex vivo* storage, or exposure to aspirin or similar drugs, uraemia and acute and chronic alcohol ingestion, may result in acquired functional compromise [19, 28, 74]. Congenitally impaired platelet function is not rare.

The next step involves the laying down of a strong fibrin mesh through the platelet plug. A sequence of proenzymes and cofactors, present in trace amounts in plasma, are concentrated on the surface of activated platelets and activated by their predecessors, and often successors, in the "cascade" (an established, if inappropriate, name: explosion is a better term) to generate the final enzyme, thrombin. Thrombin then directly cleaves the molecule fibrinogen, present in vast amounts in plasma, to produce the spontaneous, self-linking species, fibrin.

Absence or dysfunction of the factors involved in this sequence results in a coagulopathy. Congenital deficiencies are notable for being uncommon and reasonably well characterized. Predictable and well characterized acquired deficiencies or dysfunctions of the soluble clotting factors arise with anticoagulant therapy, vitamin K deficiency and liver disease. Deficiency and dysfunction of this step of coagulation form part of the complex acquired coagulopathies: disseminated intravascular coagulation (DIC), massive resuscitation, cardiopulmonary bypass and liver transplantation.

At the same time as the procoagulant mechanisms are initiated, several anticoagulant mechanisms begin, that serve to limit the extent of clotting. These anticoagulant mechanisms are the fibrinolytic system, the antithrombin pathways (one involving antithrombin III and another involving proteins C and S) and the extrinsic pathway inhibitor pathway, which inhibits the factor VIIa–thromboplastin complex. Of these mechanisms, fibrinolysis contributes to bleeding problems in surgical patients.

In the same way that clotting of fibrinogen has thrombin as its main effector, fibrinolysis has plasmin as its main enzyme. Plasmin is generated by enzymatic cleavage of the circulating inactive form, plasminogen. Plasminogen may be activated by several enzymes, of which tissue plasminogen activator (tPA) is the most important. tPA is released from endothelial cells in response to several stimuli, including thrombin. By binding to fibrinogen, it is incorporated into the clot, where it can activate fibrinogen-bound plasminogen and where it avoids rapid inactivation by potent circulating inhibitors. Normally, plasmin activity is limited by circulating inhibitors to fibrin or fibrinogen in clots, and perhaps to the platelet surface. Widespread activation of the fibrinolytic system can occur in DIC and can be achieved therapeutically by infusions of streptokinase or tPA.

Plasmin can also hydrolyse several other proteins apart from fibrinogen and fibrin, including factors V and VIII:C and the platelet membrane glycoprotein, GPIb. It is also capable of activating platelets directly [15]. Direct measurement of *in vivo* plasmin activity can be achieved by measuring specific peptides cleaved from fibrinogen by plasmin, including B-beta 1-42, B-beta 15-42, D-dimers (from fibrin crosslinked by thrombin-activated factor XIII) and fibrin(ogen) degradation products (FDP). D-dimers and FDP are the most clinically useful markers, but are affected by hepatic or renal failure. The beta peptides are suitable only for research studies.

COMPLEX ACQUIRED COAGULOPATHIES IN SURGICAL PATIENTS

Complex acquired coagulopathy may arise in many surgical settings associated with infection, severe tissue damage, massive blood loss or prolonged hypotension, or in the specific settings of cardiopulmonary bypass and liver transplantation. The patient may or may not have had a pre-existing coagulopathy associated with liver disease, drug ingestion, other co-existing disease or underlying congenital defect. In addition, more than one of these coagulopathies may arise in the same patient; for example, a degree of disseminated intravascular coagulation often complicates the coagulopathy of massive transfusion.

The complex acquired coagulopathies present difficulties in diagnosis and in management. Standard tests of coagulation are often unhelpful and may be misleading; management strategies tend to be empirical, limited and controversial.

Coagulopathy After Hypovolaemic Shock and Massive Transfusion

Patients who are being or have been resuscitated from severe haemorrhage are at risk of developing a clinically significant coagulopathy that can contribute to the morbidity and mortality of their underlying disorder. As with other bleeding disorders in surgical patients, the diagnosis is based mainly on clinical grounds, with laboratory investigation contributing subsidiary information. Even the development of a potential coagulopathy is currently better assessed by an appreciation of the recent clinical history than by the coagulation screen.

Two separate mechanisms contribute to the coagulopathy: dilution of platelets and soluble clotting factors, and consumption of platelets and factors from activation of tissue factor and tissue plasminogen activator from the ischaemic or traumatized tissues [35, 37].

Diagnosis and management

The presence of an acquired coagulopathy after hypotension and resuscitation or during treatment of massive bleeding without concurrent prolonged hypotension manifests itself clinically by diffuse oozing from the trauma or surgical wounds and by bleeding around the sites of insertion of i.v. catheters [13]. The same principles that underlie general clinical diagnostics should apply: there is usually a relevant history, and there are clinical signs as listed above. Laboratory testing should not be intended to establish the presence of a coagulopathy; this is done clinically. Instead, it should be intended to shed light on contributory or underlying mechanisms and to guide the extent, but not the nature, of therapy required.

Case history

All complex acquired coagulopathies may be worsened by pre-existing coagulopathy, such as von Willebrand's disease, thrombocytopenia or previous ingestion of aspirin or other non-steroidal anti-inflammatory drugs. However, the most relevant information is the immediate history—duration of hypotension and extent of resuscitation. Where approximately one blood volume has been replaced by infusion, a clinical coagulopathy may arise by dilutional thrombocytopenia, irrespective of any contributory effect of hypotension; by the time about two blood volumes have been replaced, a critical dilution of soluble clotting factors has been approached [17].

Laboratory investigation

Platelet count, PCV, prothrombin times (PT) and fibrinogen concentrations are important measurements to assess the extent of coagulopathy but not, as stressed above, the existence of one. In addition, these tests are poor predictions of the likelihood of onset of abnormal bleeding [13, 17]. Partial thromboplastin time (PTT) and D-dimers may be used as additional tests [13].

Coagulopathy from dilutional thrombocytopenia is usually associated with a circulating platelet count of 100×10^9 litre^{-1} or less [17]. Whether or not the measured platelets are functional is not demonstrable by routine laboratory investigations. The circulating platelets may not be functional, either because they have been activated enzymatically or degraded, or because non-functional platelets from stored blood are being counted.

Prolongation of the PT or PTT after massive transfusion in the absence of DIC is caused primarily by hypofibrinogenaemia; the presence of a consumptive coagulopathy leads to loss of other soluble factors, particularly factors V and VIII:C.

Management of coagulopathy arising during resuscitation in massive transfusion

It follows from the studies of the mechanisms of coagulopathy in these patients that bleeding should be treated, in the first instance, by platelet transfusion without a great deal of regard being paid to the circulating platelet count. In the presence of life-threatening bleeding or after head injury, a sufficient dose of platelets should be provided to attempt to increase the concentration of functional platelets towards 100×10^9 litre^{-1}. It is not possible to judge this accurately, but the required dose is about $6–8 \times 10^{11}$ platelets in an adult—about 10–12 units of platelets. Where haemorrhage is less critical, 50 % of this dose should suffice; the effect should be judged clinically.

If laboratory testing indicates that hypofibrinogenaemia or dilutional or consumptive coagulopathy is present, or when time does not allow waiting for the result, cryoprecipitate and fresh frozen plasma are required in addition to platelets when:

a) The plasma fibrinogen concentration is less than 0.8 g litre^{-1}, when fibrinogen should be replaced with cryoprecipitate: 10 units of cryoprecipitate increases the fibrinogen concentration by about 1 g litre^{-1} in an adult.

b) The PT is greater than 1.8 the normal control and the fibrinogen is greater than 0.8 g litre^{-1}, when fresh frozen plasma should be given to restore deficiencies of other clotting factors, particularly factors V and VIII:C. Two units of fresh frozen plasma (FPP) (approximately 600 ml) is the minimum dose. The effect should be monitored clinically (reversal of coagulopathy) and by laboratory testing.

The use of prophylactic infusions of plasma, or of platelets, have not been found to be justified during massive transfusions in the absence of clinical evidence of coagulopathy [13, 17].

Disseminated Intravascular Coagulation

Disseminated intravascular coagulation (DIC) arises when the physiological coagulation mechanisms that lead to thrombin and plasmin formation are triggered by pathological mechanisms in an unlocalized fashion. That is, the clotting process is not limited to wound surfaces, but it is disseminated throughout the vasculature.

The trigger that starts the procoagulant and fibrinolytic process varies. For example, amniotic fluid, brain tissue or Gram negative bacteria can directly activate the early coagulation pro-enzymes; hypotension can also initiate DIC from direct hypoxic endothelial damage that exposes tissue thromboplastin to tissue factor and plasma plasminogen to tissue plasminogen activator.

DIC may manifest clinically as: a widespread thrombotic disorder, with distal gangrene and other organ infarctions, particularly manifesting as acute renal failure; a primarily haemorrhagic disorder, caused by loss of platelets and soluble clotting factors, particularly fibrinogen, digested both by thrombin and plasmin; or a mixture of both. The severity varies from fulminant DIC with profound bleeding and thrombotic organ damage, to a mild thrombocytopenia and prolongation of clotting times that is manifest only on laboratory testing.

The heterogeneity of causes and manifestations may in part explain the lack of consensus in the management of DIC [83]. Heparin therapy has its advocates on the basis that inhibition of thrombin reduces the consumption of fibrinogen, other clotting factors and platelets, and both reduces the thrombotic element and improves the coagulation impairment. There have been no clinical trials reported that support this point of view; one clinical trial compared heparin with antithrombin III in a prospective trial in which there was no no-treatment arm. The patients treated with heparin fared worse [85].

The use of heparin in the treatment of DIC is uncommon in the U.K. Emphasis has tended towards management of bleeding or bleeding potential by correcting thrombocytopenia and deficiencies of fibrinogen and other soluble clotting factors [12, and British Committee for Standards in Haematology, in preparation], particularly the cofactors V and VIII:C, which are themselves proteolysed by plasmin. The optimum use of blood products has not been defined for DIC; however, there is no compelling evidence that suggests that replenishment of fibrinogen or platelets increases thrombotic complications of DIC, or that such products should be withheld from the surgical patient. Other products that may emerge for treatment of DIC in the future include the thrombin inhibitor, antithrombin III and the anticoagulant serine protease, activated protein C [67]. The main therapeutic objective remains rapid eradication of the precipitating cause.

An ideal therapy for DIC would be a process that impaired the pathological activity of thrombin and plasmin without impairing their physiological activities. Antithrombin III and protein C are the closest current approaches to this ideal, and further clinical studies may establish their role in this perplexing and difficult spectrum of disorders.

Liver Transplant

Orthotopic liver transplantation is accompanied by a complex coagulopathy arising from the procedure itself, complicated by the existence of a preoperative haemostatic defect that accompanies end-stage liver disease and, in some patients, hypersplenism. Liver failure *per se* is associated with impaired production of the soluble coagulation factors II, V, VII, IX, X and XI and fibrinogen, and with deficient synthesis of plasminogen and its inhibitor, alpha-1 antiplasmin. In addition, synthesis of the anticoagulant proteins C, S and antithrombin III is also reduced. A pre-existing consumptive coagulopathy or low-grade disseminated intravascular coagulation may also complicate the preoperative picture. This is because activated proteases of the coagulation pathway, together with fibrinogen degradation products, are normally cleared from the portal circulation by the liver.

Coagulopathy associated with liver failure is exaggerated during the anhepatic phase of the transplant operation. During this stage, significant fibrinolysis can result from increased tissue plasminogen activator inhibitor released from the hypoperfused distal tissues, and compounded by lack of hepatic synthesis of alpha-1 antiplasmin [20]. Thrombocytopenia may be present during the pretransplant phase, from both increased consumption and sequestration, associated with the consumptive coagulopathy and hypersplenism, respectively. These coagulopathies may be complicated further by the effects of massive transfusion.

The reasons for increased tPA activity during the anhepatic phase are uncertain and may be related to increased secretion from endothelial cells in response to the venovenous bypass procedure or hypothermia, to release of tPA from damaged tissues, or to reduced clearance of tPA as a result of the absence of hepatic function [4].

Following reperfusion of the donor liver, the coagulopathies resolve at a variable rate.

Monitoring haemostatic function in patients undergoing liver transplantation

Keeping pace with the profound and variable changes in haemostatic function during the operative stages of liver transplant is difficult. The 20–30 min that it takes to perform simple coagulation screening is too slow to be of great practical use. Some centres [53, 69] have reported useful results using thromboelastography, a somewhat old-fashioned technique that gives a rapid picture of global coagulation which includes an assessment of platelet function.

Pharmacological treatment of coagulopathy at liver transplantation

Preliminary studies have suggested that aprotinin (Trasylol, Bayer) is effective in preventing the development of coagulopathy during orthoptic liver transplantation [53, 63]. This is discussed below.

Earlier studies suggesting that antithrombin III therapy reduced blood loss in liver transplantation have not been borne out by a prospective study [6]. Although improved inhibition of thrombin activation during the transplant procedure might be expected to have some beneficial effect, the major coagulopathy probably derives from plasmin activity, which would be influenced by aprotinin, but not by antithrombin III.

Cardiopulmonary Bypass

Recent studies have demonstrated that the use of large doses of the drug aprotinin reduces the blood loss and coagulopathy associated with cardiopulmonary bypass. The mechanism of action of aprotinin remains unclear and the failure of previous theories of the pathophysiology of coagulopathy caused by cardiopulmonary bypass to predict the effect of aprotinin, has cast considerable doubt on the validity of previous interpretations of the observed phenomenon.

Clinical studies

In 1987, Royston and co-workers reported that large doses of aprotinin, given to patients undergoing repeat cardiopulmonary bypass procedures for valve replacement, resulted in a considerably lesser degree of coagulopathy and reduced blood requirements compared with those of control patients [73]. Other studies have confirmed these findings and extended them to patients with septic endocarditis [66] and to patients who had ingested aspirin shortly before surgery [9]. Use of aprotinin in cardiopulmonary bypass surgery has since become widespread. Aprotinin had been used in cardiopulmonary bypass in the 1960s and 70s without convincing evidence of effect. The difference between present and current regimens is the dose used: currently a loading dose of up to 2000000 kallekrein inhibitory units (KIU) is used, followed by an infusion of 500000 KIU h^{-1} until the end of bypass, whereas formerly about 50% of this dose was used.

The investigators who described this effect of high-dose aprotinin on blood loss in cardiac surgery had not set out to look for one. Their intention had been to demonstrate a beneficial effect of aprotinin on pulmonary function after cardiopulmonary bypass.

Causes of coagulopathy in cardiopulmonary bypass in relation to the mechanisms of action of aprotinin

Many detrimental effects of cardiopulmonary bypass on the coagulation systems have been reported. The most prominent effects have been on platelets: loss of membrane structures and granule contents, and generation of activation markers on the platelet surface [2, 27, 60, 88, 89]. Additional observed effects have included activation of the fibrinolytic system and of the contact system, and activation of leucocytes with release of granule contents [14, 32, 38, 86, 87].

The mechanism of action of aprotinin in preventing the coagulopathy of cardiopulmonary bypass remains unclear. However, clinical studies have demonstrated or suggested a protective effect against haemorrhage in surgical situations other than cardiopulmonary bypass, including liver transplantation and vascular surgery [53, 84]. This suggests that the effect of aprotinin is not limited to cardiopulmonary bypass alone, and that it is not attributable to prevention of platelet activation in the pump mechanism. Future data may indicate that use of aprotinin leads to amelioration of physiological haemostasis in other conditions.

The fact that previous observations or measurements of the function of the coagulation systems did not lead directly to the conclusion that a protease inhibitor would prevent the changes induced by cardiopulmonary bypass, indicates that many or all such observations were of events downstream to some initial event that is preventable by aprotinin. Until such time as monofunctional drugs are available that selectively impair one enzymatic function at one site in the coagulation system, the site of action of aprotinin will remain speculative. Notwithstanding this, a likely candidate for future examination of the prime site of action of aprotinin is platelet membrane GPIb. Van Oeveren and colleagues [65] have shown that loss of GPIb is an early event during cardiopulmonary bypass that is prevented by aprotinin in clinical studies.

As GPIb–von Willebrand factor adhesion is of fundamental importance in the very early stages of coagulation, it is possible that its preservation on the surface contributes to the haemostatic effect of aprotinin. In addition, GPIb contains the thrombin binding site involved in thrombin-induced activation of platelets [36], so that subsequent ability of platelets to respond to thrombin stimulation is possibly increased. Perhaps of more importance, hydrolysis of GPIb by aprotinin-inhibited enzymes generated during the coagulation/fibrinolysis processes may itself result in platelet activation. The prevention of such activation may preserve the circulating platelets from further damage in the bypass circuit. This is because platelets will not then have on their surface functional fibrinogen binding sites (induced by prior activation) that would promote binding of platelets to fibrinogen deposited in the bypass tubing.

GPIb is a transmembrane heterodimer; the external portion is readily cleaved from the platelet surface by plasmin, elastase and calpain. All of these enzymes can be inhibited by aprotinin, and all are direct platelet agonists in addition to, or perhaps because of, their ability to cleave GPIb.

Plasmin. Plasmin activity in cardiopulmonary bypass has been demonstrated in several studies [86]. This activity can be generated through tissue plasminogen activator from endothelial cells or from scar tissue at sternotomy or other surgical procedure, or through activation of the contact system. Contact system activation does occur during the bypass phase: its role is unclear in the generation of coagulopathy or in the prevention of that coagulopathy by aprotinin, as the presence of bypass circuitry may not be essential for aprotinin to have a haemostatic effect. However, it is important to note that both plasminogen and a plasminogen activator, SCU-plasminogen activator, are present on the platelet surface [56, 70]; in the presence of kallekrein generated by the contact system, plasmin could be generated directly on the platelet surface by direct activation of SCU-plasminogen activator.

Elastase. Neutrophil elastase is generated from activated neutrophils during cardiopulmonary bypass. Elastase can cleave GPIb and is a direct platelet agonist [40]. It is inhibited by aprotinin [25], but at greater concentrations than are required for inhibition of plasmin.

Calpain. Calpain is a cysteine protease present in many cells including red cells and platelets, where it comprises about 2% of total platelet intracellular protein. It is present in active form on the surface of thrombin-stimulated platelets and, possibly, plasmin-stimulated platelets [15]. It can cleave GPIb from the platelet surface *in vitro* [51] and *in vivo* [58], and is a direct platelet agonist. In addition, it cleaves the ADP receptor, aggregin [15]. It is inhibited by aprotinin in solution [52] and on the platelet surface [59].

Other mechanisms by which aprotinin could contribute to improved haemostatic function

By preventing dissolution of formed fibrin clots (through its ability to inhibit plasmin) or by preventing the self-inhibition of thrombin via protein C [22], aprotinin could improve clot formation and prevent its dissolution. Any benefit from such activity is likely to be modest. Fibrinolysis is usually normal at the end of bypass [32] and fibrin generation is not significantly impaired.

In conclusion, aprotinin may exert its effect by one or more of several mechanisms. Exploration of events occurring very early in the coagulation systems is likely to be most informative; inhibition of tPA-induced plasmin on the platelet surface could account for much or all of the observed benefit.

Coagulopathy Complicating Rupture of Abdominal Aortic Aneurysm

Mortality from ruptured abdominal aortic aneurysm has been strongly associated with coagulopathy and uncontrollable haemorrhage [29, 55, 57]. This mortality has risen progressively over the past 20 years [24, 62] and is the commonest life-threatening emergency in vascular surgery and a major consumer of surgical intensive care resources [G. C. Davies, personal communication]. In those patients who reach hospital, the operative mortality is in the range 21–70%, with a mean of about 50% [16, 68, 76]. After operation, haemorrhage and multi-system organ failure are major causes of morbidity and mortality [29, 30].

While the development of coagulopathy is causally associated with other conditions contributing to increased risk (including time for resuscitation, larger surgical bleeds, more extensive surgical procedures and renal failure) the development of excessive bleeding has been reported as an important cause of death in these patients [29, 55, 57]. The abnormal bleeding is the result of disseminated intravascular coagulation or dilution of procoagulant factors, or a combination of both. Clinical observations suggest that there are two categories among these patients who present with ruptured abdominal aortic aneurysm. The first group has a low mortality rate and may be considered to be well managed by current therapy [3, 80]. The second patient group has a mortality of 70–100% [80]. Early identification of these high risk patients at an early stage offers a prospect of trialling new and, if necessary, radical approaches to management.

In a recent prospective study [7], 23 consecutive patients with ruptured aneurysms had a coagulation screen performed immediately on admission to the accident and emergency department: six of 13 patients with an abnormal screen died, compared with none of 10 patients with normal screens ($P = 0.04$, chi-square test with Yates' correction). These observations are similar to previous published experience in which the mortality of patients with acquired coagulopathy was 11 of 15 [29], eight of nine [55] and four of four patients [57].

It remains to be demonstrated that correction of coagulopathy present on admission in these patients will result in improved outcome. Previous attempts to prevent the onset of coagulopathy in surgical patients receiving massive transfusion using prophylactic platelet transfusions and fresh frozen plasma have not been successful. However, it is possible that early and aggressive attempts to reverse the tissue hypoxia and prevent the subsequent coagulopathy in these patients may result in an overall improvement in outcome.

USE OF FIBRIN GLUE AS A HAEMOSTATIC AGENT IN SURGERY

Fibrin glue has been used in a wide range of surgical procedures. It works by a simple process. Direct application of formed fibrin onto the bleeding site bypasses physiological requirements for haemostasis. The glue is prepared as two separate solutions, one of fibrinogen and the other of thrombin. These two agents are mixed at or near the required site of action and rapidly form an adherent fibrin plug. The rate of formation of fibrin can be regulated by altering the concentration of thrombin. Fibrin glue may delay nerve and bone repair [49, 61], but other potential complications such as viral transmission, adhesion formation and unwanted thrombosis remain theoretical.

Fibrin glue has been reported to be effective in cardiovascular and general vascular surgery, in paediatric cardiovascular surgery and in thoracic, plastic, oral, ENT, neurosurgical, splenic, hepatic and orthopaedic surgery [5, 11, 23, 31, 33, 39, 41–43, 46, 48, 50, 54, 61, 64, 71, 78, 79, 81, 82, 90]. The evidence for its efficacy has been compelling, especially where fibrin sealant has been used in surgery in patients with acquired or congenital coagulation disorders [41,48]. However, prospective controlled clinical trials have been few and benefit has often been reported by anecdote or impression.

A large prospective clinical trial of fibrin sealant was reported by Rousou and colleagues [72]. Patients undergoing sternotomy were allocated randomly to receive either treatment with fibrin sealant (Tisseel, Immuno AG, Austria) or conventional haemostatic topical agents (Avitene, Gelfoam, Oxycel, Surgicel, or Thrombinar). A success rate of more than 90% was reported in achieving haemostasis within 5 min from the fibrin sealant, regardless of whether the patient had received heparin. In comparison, a 12.4% success rate was achieved with conventional therapy.

CONCLUSION

It is now apparent that it is possible to augment physiological haemostasis in surgical patients by pharmacological means including aprotinin and fibrin sealant. The next few years may see an extension of these techniques to many surgical fields.

REFERENCES

1. Aberg M, Hedner U, Bergentz SE. The antithrombotic effect of dextran. *Scandinavian Journal of Haematology* 1979; (Suppl. 34): 61–68.
2. Addonizio VP jr, Smith JB, Guiod LR, Strauss JF, Colman RW, Edmunds LH. The relationship between thromboxane synthesis and platelet protein release during simulated extracorporeal circulation. *Blood* 1979; **54**: 371–376.
3. Amudsen S, Skjaerven R, Trippestad A, Soreide O. Abdominal aortic aneurysms—a study of factors influencing postoperative mortality. *European Journal of Vascular Surgery* 1989; **3**: 405–409.
4. Arnoux D, Boutiere B, Houvenaeghel M, Rousset-Rouviere A, Le Treut P, Sampol J. Intraoperative evolution of coagulation parameters and t-PA/PAI balance in orthotopic liver transplantation. *Thrombosis Research* 1989; **55**: 319–328.
5. Baudo F, De Cataldo F, Landonio G, Muti G. Management of oral bleeding in haemophilic patients. *Lancet* 1988; **2**: 1082.
6. Baudo F, De Gasperi A, Belli L, De Cataldo F. Antithrombin III, blood loss, and transfusion requirements during liver transplantation. *Lancet* 1991; **338**: 897–898.
7. Bell K, Gray S, Callum M, Gillon J. Audit of supply of blood to patients with ruptured abdominal aortic aneurysm. *Transfusion Medicine* 1991; **1** (Suppl. 2): 84.
8. Bessos H, Murphy WG. A new competitive binding enzyme-linked immunosorbent assay for glycocalicin in plasma and platelet concentrate supernatants. *Thrombosis Research* 1990; **59**: 497–507.
9. Bidstrup BP, Royston D, Sapsford RN, Taylor KM. Reduction in blood loss and blood use after cardiopulmonary bypass with high-dose aprotinin (Trasylol). *Journal of Thoracic and Cardiovascular Surgery* 1989; **97**: 364–372.
10. Bolin RB, Medina F, Cheney BA. Glycoprotein changes in fresh *vs* room temperature-stored platelet and their buoyant density cohorts. *Journal of Laboratory and Clinical Medicine* 1981; **98**: 500–510.
11. Borst HG, Haverich A, Walterbusch G, Maatz W. Fibrin adhesive: an important hemostatic adjunct in cardiovascular operations. *Journal of Thoracic and Cardiovascular Surgery* 1982; **84**: 548–553.
12. British Committee for Standards in Haematology. Guidelines for the use of fresh frozen plasma. *Transfusion Medicine* 1992; **2**: 57–63.
13. Ciavarella D, Reed RL, Counts RB, Baron L, Pavlin E, Heimbach DM, Carrico CJ. Clotting factor levels and the risk of diffuse microvascular bleeding in the massively transfused patient. *British Journal of Haematology* 1987; **67**: 365–368.
14. Colman RW. Platelet and neutrophil activation in cardiopulmonary bypass. *Annals of Thoracic Surgery* 1990; **49**: 32–34.
15. Colman RW, Puri RN, Zhou F, Colman RF. Mechanism of plasmin-induced platelet aggregation. In: Patrono C, FitzGerald GA, eds. *Platelets and Vascular Occlusion*. New York: Raven Press, 1988; 279–285.
16. Cooley DA, Carmichael MJ. Abdominal aortic aneurysm. *Circulation* 1984; **70** (Suppl. 1): 5–6.
17. Counts RB, Haisch C, Simon TL, Maxwell NG, Heimbach DM, Carrico CJ. Haemostasis in massively transfused trauma patients. *Annals of Surgery* 1979; **190**: 91–99.
18. Devine DV, Currie MS, Rosse WF, Greenberg CS. Pseudo-Bernard–Soulier syndrome: thrombocytopenia caused by autoantibody to platelet glycoprotein Ib. *Blood* 1987; **70**: 428–431.
19. Deykin D, Janson P, McMahon L. Ethanol potentiation of aspirin-induced prolongation of the bleeding time. *New England Journal of Medicine* 1982; **306**: 852–854.
20. Dzik WH, Arkin CF, Jenkins RL, Stump DC. Fibrinolysis during liver transplantation in humans: role of tissue-type plasminogen activator. *Blood* 1988; **71**: 1090–1095.
21. Escolar G, Garrido M, Mazzara R, Castillo R, Ordinas A. Experimental basis for the use of red cell transfusion in the management of anemic–thrombocytopenic patients. *Transfusion* 1988; **28**: 406–411.
22. Espana F, Estelles A, Griffin JH, Asnar J, Gilabert J. Aprotinin (Trasylol) is a competitive inhibitor of activated protein C. *Thrombosis Research* 1989; **56**: 751–756.
23. Fabiani J-N, Jebara VA, DeLoche A, Carpentier A. Use of glue without graft replatement for type A dissections: a new surgical technique. *Annals of Thoracic Surgery* 1990; **50**: 143–145.
24. Fowkes FGC, Macintyre CCA, Ruckley CV. Increasing incidence of aortic aneurysms in England and Wales. *British Medical Journal* 1989; **298**: 33–35.
25. Fritz H, Wunderer G. Biochemistry and applications of aprotinin, the kallikrein inhibitor from bovine organs. *Arzneimittel-Forschung* 1983; **33**: 479–494.
26. George JN. Platelet membrane glycoproteins: alteration during storage of human platelet concentrates. *Thrombosis Research* 1976; **8**: 719–724.
27. George JN, Picket EB, Saucerman S, McEver RP, Kunicki TJ, Kieffer N, Newman PJ. Platelet surface glycoproteins: studies on resting and activated platelets and platelet microparticles in normal subjects and observations in patients during adult respiratory distress syndrome and cardiac surgery. *Journal of Clinical Investigation* 1986; **78**: 40–48.
28. George JN, Shattil SJ. The clinical importance of acquired abnormalities of platelet function. *New England Journal of Medicine* 1991; **324**: 27–39.
29. Getaz EP, Louw JH. The coagulopathy associated with aortic aneurysms. *Postgraduate Medical Journal* 1977; **53**: 668–671.
30. Gibney EJ, Bouchier-Hayes D. Coagulopathy and abdominal aortic aneurysm. *European Journal of Vascular Surgery* 1990; **4**: 557–562.
31. Goldman CD, Blocker SH, Ternberg JL, Crouch EC. Management of experimental pneumothorax in weanling rabbits with the use of fibrin glue sclerosant. *Archives of Surgery* 1986; **121**: 565–568.
32. Gralnick HR, Fischer RD. The hemostatic response to open-heart operations. *Journal of Thoracic and Cardiovascular Surgery* 1971; **61**: 909–915.
33. Gundry SR, Behrendt DM. A quantitative and qualitative comparison of fibrin glue, albumin, and blood as agents to pretreat porous vascular grafts. *Journal of Surgical Research* 1987; **43**: 75–77.
34. Harfenist EJ, Packham MA, Kinlough-Rathbone RL, Cattaneo M, Mustard JF. Effect of calcium ion concentration on the ability of fibrinogen and von Willebrand factor to support the ADP-induced aggregation of human platelets. *Blood* 1987; **70**: 827–831.
35. Harke H, Rahman S. Haemostatic disorders in massive transfusion. *Bibliotheca Haematologica* 1980; **46**: 179–188.
36. Hamron JT, Jamieson GA. The glycocalicin portion of platelet glycoprotein Ib expresses both high and moderate affinity receptor sites for thrombin: a soluble radioreceptor assay for the interaction of thrombin with platelets. *Journal of Biological Chemistry* 1986; **261**: 13224–13229.

37. Hewson JR, Neame PB, Kumar N, Ayrton A, Gregor P, Davis C, Shragge BW. Coagulopathy related to dilution and hypotension during massive transfusion. *Critical Care Medicine* 1985; **13**: 387–391.
38. Hind CRK, Griffin JF, Pack S, Latchman YE, Drake HF, Jones HM, Brostoff J, Dormandy TC, Treasures T. Effect of cardiopulmonary bypass on circulating concentrations of leucocyte elastate and free radical activity. *Cardiovascular Research* 1988; **22**: 37–41.
39. Jessen C, Sharma P. Use of fibrin glue in thoracic surgery. *Annals of Thoracic Surgery* 1985; **39**: 521–524.
40. Kornecki E, Ehrlich YH, De Mars DD, Lenox RH. Exposure of fibrinogen receptors in human platelets by surface proteolyis with elastase. *Journal of Clinical Investigation* 1986; **77**: 750–756.
41. Kram HB, Nathan RC, Stafford FJ, Fleming AW, Shoemaker WC. Fibrin glue achieves hemostasis in patients with coagulation disorders. *Archives of Surgery* 1989; **124**: 385–387.
42. Kram HB, Shoemaker WC, Hino ST, Chiang HS, Harley DP, Fleming AW. Tracheal repair with fibrin glue. *Journal of Thoracic and Cardiovascular Surgery* 1985; **90**: 771–775.
43. Kram HB, Shoemaker WC, Hino ST, Harley DP. Splenic salvage using biological glue. *Archives of Surgery* 1984; **119**: 1309–1311.
44. Kroll MH, Harris TS, Moake JL, Handin RI, Schafer AI. Von Willebrand factor binding to platelet GPIb initiates signals for platelet activation. *Journal of Clinical Investigation* 1991; **88**: 1568–1573.
45. Kroll MH, Schafer AI. Biochemical mechanisms of platelet activation. *Blood* 1989; **74**: 1181–1195.
46. Lilius P. Fibrin adhesive: its use in selected skin grafting. Practical note. *Scandinavian Journal of Plastic and Reconstructive Surgery and Hand Surgery* 1987; **21**: 245–248.
47. Lind SE. Prolonged bleeding time. *American Journal of Medicine* 1984; **77**: 305–312.
48. Lindsey WH, Masterton TM, Llancras M, Spotnitz WD, Wanebo HJ, Morgan RF. Seroma prevention using fibrin glue during modified radical neck dissection in a rat model. *American Journal of Surgery* 1988; **156**: 310–313.
49. Lucht U, Bunger C, Moller JT, Joyce F, Plenk H. Fibrin sealant in bone transplantation. No effects on blood flow and bone formation in dogs. *Acta Orthopaedica Scandinavica* 1986; **57**: 19–24.
50. McCarthy PM, Trastek VF, Bell DG, Butterman GR, Piehler JM, Payne WS, Weiland LH, Pairolero PC. The effectivness of fibrin glue sealant for reducing experimental pulmonary air leak. *Annals of Thoracic Surgery* 1988; **45**: 203–205.
51. McGowan EB, Yeo K-T, Detwiler TC. The action of calcium-dependent protease on platelet surface glycoproteins. *Journal of Biochemistry and Biophysics* 1983; **22**: 287–301.
52. Malik MN, Ramaswamy S, Tuzio H, Sheik AM, Fenko MD, Wisniewski HM, Howard RG. Micromolar Ca^{2+} requiring protease from human platelets: purification, partial characterization and effect on the cytoskeletal proteins. *Life Sciences* 1987; **40**: 593–604.
53. Mallett SV, Cox D, Burroughs AK, Rolles K. Aprotinin and reduction of blood loss and transfusion requirements in orthotopic liver transplantation. *Lancet* 1990; **336**: 886–887.
54. Margarit C, Martinez-Ibanez V, Lloret J, Ventura H, Broto J, Isnard R, Blanco J, Allende H. Segmental liver transplantation in pigs: use of fibrin sealant and collagen as hemostatic agents. *Transplantation Proceedings* 1987; **19**: 3835–3837.
55. Marsh CH. Experience with abdominal aortic aneurysms in a district general hospital. *Annals of the Royal College of Surgeons of England* 1980; **62**: 294–296.
56. Miles LA, Plow EF. Binding and activation of plasminogen on the platelet surface. *Journal of Biological Chemistry* 1985; **206**: 4303.
57. Mulcare RJ, Royster TS, Weiss HJ, Phillips LL. Disseminated intravascular coagulation as a complication of abdominal aortic aneurysm repair. *Annals of Surgery* 1974; **180**: 343–349.
58. Murphy WG, Moore JC, Kelton JG. Calcium-dependent cysteine protease activity in the sera of patients with thrombotic thrombocytopenic purpura. *Blood* 1987; **70**: 1683–1687.
59. Murphy WG, Moore JC, Warkentin T, Kelton JG. Aprotinin inhibits calpain-induced proteolysis of GPIb on the platelet surface. *Schweizerische Medizinische Wochenschrift* 1991; **121** (Suppl. 43): 130.
60. Musial J, Niewiarowski S, Hershock D, Morinelli TA, Colman RW, Edmunds LH jr. Loss of fibrinogen receptors from the platelet surface during simulated extracorporeal circulation. *Journal of Laboratory and Clinical Medicine* 1985; **105**: 514–522.
61. Narakas A. The use of fibrin glue in repair of peripheral nerves. *Orthopedic Clinics of North America* 1988; **19**: 187–199.
62. Naylor AR, Webb J, Fowkes FGR, Ruckley CV. Trends in abdominal aortic aneurysm surgery in Scotland (1971–1984). *European Journal of Vascular Surgery* 1988; **2**: 217–222.
63. Neuhaus P, Bechstein WO, Lefebre B, Blumhardt G, Slama K. Effect of aprotinin on intraoperative bleeding and fibrinolysis in liver transplantation. *Lancet* 1989; **2**: 924–925.
64. Nishihira S, McCaffrey TV. The use of fibrin glue for the repair of experimental CSF rhinorrhea. *Laryngoscope* 1988; **98**: 625–627.
65. van Oeveren W, Harder MP, Roozendaal KJ, Eljsman L, Wildevuur CR. Aprotinin protects platelets against the initial effect of cardiopulmonary bypass. *Journal of Thoracic and Cardiovascular Surgery* 1990; **99**: 788–797.
66. van Oeveren W, Jansen NJG, Bistrup BP, Royston D, Westaby S, Neuhof H, Wildevuur CRH. Effects of aprotinin on hemostatic mechanisms during cardiopulmonary bypass. *Annals of Thoracic Surgery* 1987; **44**: 640–645.
67. Okajima K, Imamura H, Koga S, Inoue M, Takatsuki K, Aoki N. Treatment of patients with disseminated intravascular coagulation by protein C. *American Journal of Hematology* 1990; **33**: 277–278.
68. Ouriel K, Geary K, Green RM, Fiore W, Geary JE, De Weese JA. Factors determining survival after ruptured aortic aneurysm: the hospital, the surgeon and the patient. *Journal of Vascular Surgery* 1990; **11**: 493–496.
69. Owen CA jr, Rettke SR, Bowie EJW, Cole TL, Jewsew CC, Weisner RH, Krom RA. Hemostatic evaluation of patients undergoing liver transplantation. *Mayo Clinic Proceedings* 1987; **62**: 761–772.
70. Park S, Harker LA, Marzec UM, Levin EG. Demonstration of single chain urokinase-type plasminogen activator on human platelet membrane. *Blood* 1989; **73**: 1421–1425.
71. Pini Prato GP, Cortellini P, Agudio G, Clauser C. Human fibrin glue versus sutures in periodontal surgery. *Journal of Periodontal Surgery* 1987; **58**: 426–431.
72. Rousou J, Gonzalez-Lavin L, Cosgrove D, Weldon C, Hess P, Joyce L, Bergsland J, Gazzaniga A. Randomized clinical trial of fibrin sealant in patients undergoing resternotomy or reoperation after cardiac operations. *Journal of Thoracic and Cardiovascular Surgery* 1989; **97**: 194–203.
73. Royston D, Bidstrup BP, Taylor KM, Sapsford RN. Effect of aprotinin on need for blood transfusion after repeat open-heart surgery. *Lancet* 1987; **2**: 1289–1291.
74. Rubin R. Effects of ethanol on platelets. *Laboratory Investigation* 1990; **63**: 729–732.
75. Ruggeri ZM, De Marco L, Gatti L, Bader R, Montgomery RR. Platelets have more than one binding site for von Willebrand factor. *Journal of Clinical Investigation* 1983; **72**: 1–12.
76. Salo JA, Perhoneimi VJ, Mauri JA, Lepantalo MJ, Mattica PS. Prognosis of patients over 75 years of age with a ruptured aortic aneurysm. *World Journal of Surgery* 1989; **13**: 484–487.
77. Salzman EW, Weinstein MJ, Weintraub RM, Ware JA, Thurer RL, Robertson L, Donovan A, Gaffney T, Bertele V, Troll J, Smith M, Chute L. Treatment with desmopressin acetate to reduce blood loss after cardiac surgery: a double-blind randomized trial. *New England Journal of Medicine* 1986; **314**: 1402–1406.
78. Scheele J, Gentsch HH, Matteson E. Splenic repair by fibrin tissue adhesive and collagen fleece. *Surgery* 1984; **95**: 6–13.
79. Schlag G, Redl H. Fibrin sealant in orthopaedic surgery. *Clinical Orthopaedics* 1988; **227**: 269–285.
80. Shackleton CR, Schechter MT, Bianco R, Hildebrand HD. Preoperative predictors of mortality in ruptured abdominal aortic aneurysm. *Journal of Vascular Surgery* 1987; **6**: 583–589.

81. Spotnitz WD, Dalton MS, Baker JW, Nolan SP. Reduction of perioperative hemorrhage by anterior mediastinal spray application of fibrin glue during cardiac operations. *Annals of Thoracic Surgery* 1987; **44**: 529–531.
82. Stark J, de Leval M. Experience with fibrin seal (Tisseel) in operations for congenital heart defects. *Annals of Thoracic Surgery* 1984; **38**: 411–412.
83. Takahashi H, Tatewaki W, Wada K, Hanano M, Shibata A. Thrombin *vs* plasmin generation in disseminated intravascular coagulation associated with various underlying disorders. *American Journal of Hematology* 1990; **33**: 90–95.
84. Thompson JF, Roath OS, Francis JL, Webster JHH, Chant ADB. Aprotinin in peripheral vascular surgery. *Lancet* 1990; **335**: 911.
85. Vinazzer H. Clinical use of antithrombin III concentrates. *Vox Sanguinis* 1987; **53**: 193–198.
86. Wachtfogel YT, Harpel PC, Edmunds LH jr, Colman RW. Formation of C1s-C1-inhibitor, kallikrein-C1-inhibitor and plasma-alpha$_2$-plasmin-inhibitor complexes during cardiopulmonary bypass. *Blood* 1989; **73**: 468–471.
87. Wachtfogel YT, Kucich U, Greenplate J, Gloszko P, Abrams W, Weinbaam G, Wenger RK, Rucinski B, Niewiarowski S, Edmunds H jr, Colman RW. Human neutrophil degranulation during extracorporeal circulation. *Blood* 1987; **69**: 324–330.
88. Wachtfogel YT, Musial J, Jenkin B, Niewiarowski S, Edmunds LH jr, Colman RW. Loss of platelet alpha 2-adrenergic receptors during simulated extracorporeal circulation: prevention with prostaglandin E1. *Journal of Laboratory and Clinical Medicine* 1985; **105**: 601–607.
89. Wenger RK, Lukasiewicz H, Mikuta BS, Niewiarowski S, Edmunds LH jr. Loss of platelet fibrinogen receptors during clinical cardiopulmonary bypass. *Journal of Thoracic and Cardiovascular Surgery* 1989; **97**: 235–239.
90. Wolner E. Fibrin glueing in cardiovascular surgery. *Thoracic and Cardiovascular Surgery* 1982; **30**: 236–237.

British Journal of Anaesthesia 1993; 70: 214–215

SHORT COMMUNICATIONS

LONG-TERM BACKACHE AFTER EXTRADURAL OR GENERAL ANAESTHESIA FOR MANUAL REMOVAL OF PLACENTA: PRELIMINARY REPORT

R. J. VICKERS AND A. E. MAY

A questionnaire designed to investigate the incidence of newly acquired, long-term backache was sent to women who had previously undergone manual removal of the placenta during a 12-month period in one maternity hospital. There was a significantly greater incidence of long-term backache in patients who had extradural anaesthesia specifically for manual removal of the placenta compared with patients receiving a general anaesthetic for the same procedure. The results of this retrospective study in a small population warrant examination in a large, prospective, controlled investigation. (Br. J. Anaesth. 1993; **70**: 214–215)

KEY WORDS

Anaesthesia, general. Anaesthesia, obstetric. Anaesthetic techniques: extradural. Complications: backache.

A large retrospective study examining the incidence of long-term backache after childbirth found that the incidence was significantly greater in those patients who had an extradural sited during labour than in those who had either no extradural during labour or an extradural sited only for an elective Caesarean section [1]. The authors postulated that the increased incidence of backache after an extradural in labour resulted from inadvertent stressed posture resulting from the combination of effective analgesia and muscle relaxation.

To clarify further the relative significance of stressed posture, labour and extradurals in the causation of long-term backache, we have examined the incidence of long-term backache after extradural and after general anaesthesia for manual removal of placenta. Patients in this group would not have had the combination of stressed posture and extradural analgesia in labour.

PATIENTS AND RESULTS

The study was approved by the local Ethics Committee. A questionnaire was sent in September 1991 to all patients recorded in the birth register as having undergone manual removal of the placenta between March 1, 1990 and February 28, 1991.

The questionnaire comprised the following:

1. What type of anaesthetic did you have?
   General (put to sleep) — Extradural (injection in back)
2. If you had an extradural, when was it put in?
   Before delivery of baby/after delivery of baby

Since delivery, have you had any of the following problems:

3. *Headache* Yes/No
   (If "no" go to Question 4)
   If "yes"
   How often do you get them
   Are they worse than before delivery? Yes/No
   Have you needed to see a doctor about them? Yes/No
4. *Backache*
   (If "no" go to Question 5)
   How long after delivery did the backache start?
   When did you stop having backache?
   Have you needed to see your doctor about it? Yes/No
   Had you ever seen a doctor about backache before you were pregnant this time? Yes/No
5. *Numbness in your legs* Yes/No
   If "yes"
   How long after delivery did it start?
   When did it end?
   Did you see a doctor about it? Yes/No

If no reply was received, a second identical questionnaire with a covering letter was sent in January 1992.

A total of 98 questionnaires were sent. There was a response of 68 replies to the first mailing and a further eight to the second. This total of 77 replies represents a response rate of 78.57%.

The questionnaires revealed that, of the 77 responders, 19 had a general anaesthetic and 55 had an extradural for manual removal of the placenta. Of these 55, 17 had the extradural sited in labour before delivery of the baby and 38 after. Of the remaining three, two received only Entonox for manual removal of the placenta and one had an unsuccessful extradural and required a general anaesthetic.

We have compared the 19 patients who had a general anaesthetic and the 38 patients who had an extradural anaesthetic sited specifically for manual removal of the placenta.

We defined significant backache as a period of at

RACHEL J. VICKERS, M.B., CH.B.; ANNE E. MAY, F.R.C.ANAES.; Department of Anaesthesia, Leicester Royal Infirmary, Leicester LE1 5WW. Accepted for Publication: September 23, 1992.

TABLE I. *Incidence of backache in the two groups*

	General anaesthesia	Extradural anaesthesia
Total No. patients	17	33
Significant backache (No. (%))	1 (6.25)	11 (33.3)

least 6 weeks of backache occurring within 3 months of delivery [1]. None of the patients had previously suffered from backache, apart from one who had a general anaesthetic. Two patients who had undergone general anaesthesia and five patients who had undergone extradural anaesthesia after delivery of the baby gave insufficient information in response to the questionnaire to determine if the backache was significant (as defined above). These eight patients were excluded from analysis.

There was a significant difference in the incidence of backache between the two groups ($P = 0.04$, Fisher's exact probability test) (table I).

COMMENT

Backache is a common problem; according to the U.K. Department of Health, 46.5 million working days are lost each year. Amongst female sufferers, many trace the onset of backache to childbirth, and some to extradural analgesia in particular, but this has not been subjected to close examination.

Large numbers of extradural blocks are performed in the peripartum period, but little is known about the incidence of long-term effects from such blocks. MacArthur and colleagues [1] have published the only study on long-term backache after extradural analgesia in labour. They found that those women who had received an extradural block in labour had a significantly greater incidence of long-term backache. However, this study was retrospective and not randomized. The lack of data on extradural blocks in obstetrics from prospective randomized trials has been highlighted recently [2].

In this study, we have found a significant difference in the incidence of backache between those undergoing general anaesthesia and those having an extradural for manual removal of placenta. This suggests that the increased incidence of long term backache was caused by the extradural block itself and not stressed posture as suggested by McArthur and colleagues [1]. However, our study suffers from the limitations of being small, retrospective and not randomized. Whilst it would be difficult to randomize patients, during labour, to receive extradural analgesia or another mode of analgesia, it should be possible for manual removal of placenta. The purpose of publishing our preliminary data is to draw attention to this important problem and encourage the performance of large-scale prospective, randomized studies to determine if long-term backache is a real and important sequela of extradural analgesia in obstetric practice.

REFERENCES

1. MacArthur C, Knox EG, Lewis M, Crawford JS. Epidural anaesthesia and long term backache after childbirth. *British Medical Journal* 1990; 301: 9–12.
2. Howell C, Chalmers I. A review of prospective controlled comparisons of epidural with non-epidural forms of pain relief during labour. *International Journal of Obstetric Anaesthesia* 1992; 1: 93–110.

British Journal of Anaesthesia 1993; **70**: 216–218

CLINICAL EVALUATION OF THE OESOPHAGEAL HEAT EXCHANGER IN THE PREVENTION OF PERIOPERATIVE HYPOTHERMIA

P. KULKARNI, A. MATSON, J. BRIGHT, J. PEARSON AND F. CARLI

SUMMARY

We have studied the efficiency of an oesophageal warming device in the prevention of perioperative hypothermia in 22 patients undergoing total hip replacement. Aural canal and skin temperatures (15 sites) were measured before induction of anaesthesia, at the end of surgery and 1 h after recovery and mean body heat was calculated to quantify heat distribution. Core temperature decreased significantly in both groups at the end of surgery, by a mean of 1.8 °C in the control group and 1.3 °C in the oesophageal heat exchanger (treated) group (P = 0.09). In contrast, mean skin temperature at the end of surgery increased by a median value of 0.26 °C in the treated group and decreased by 1.02 °C in the control group (P = 0.03). Both groups of patients lost body heat to the same extent (P = 0.34). Thus the oesophageal heat exchanger was ineffective in preventing perioperative hypothermia in a group of patients undergoing total hip replacement. (Br. J. Anaesth. 1993; **70**: 216–218)

KEY WORDS

Hypothermia: perioperative. Equipment: oesophageal warmer. Temperature: body.

Heat loss can occur during anaesthesia and surgery, and the resultant hypothermia might lead to increased morbidity and mortality, especially in the high risk population, such as the elderly with poor cardiovascular reserves [1].

The oesophagus is a convenient site for core (central) warming in anaesthetized patients, being easily accessible and situated in close proximity to the major blood vessels, thus acting as a good conduit for heat transfer. An oesophageal thermal device has been designed and shown to be effective in delivering heat and in the prevention of perioperative hypothermia [2].

We have examined the efficacy of the oesophageal warming device in the prevention of perioperative hypothermia in patients undergoing total hip replacement in a cool operating environment, by measuring core (tympanic) and skin temperatures at 15 sites.

METHODS AND RESULTS

After obtaining Ethics Committee approval and informed consent, we studied 22 patients (ASA I and disease, undergoing elective unilateral total hip replacement. They were randomly allocated to two groups: a control group ($n = 11$) (median age 73 yr (range 34–83 yr); weight 64 kg (range 48–90 kg)), with no active warming technique in the intraoperative period and a treated group ($n = 11$) (median age 71 yr (range 52–82 yr); weight 66 kg (range 46–90 kg)) using the oesophageal heat exchanger system.

The oesophageal thermal tube (Granulab, Pennco Medicals Ltd, London) was tested before each study for water leaks, obstruction in the connections and any evidence of damage. After induction of anaesthesia and tracheal intubation, a well lubricated oesophageal thermal tube was inserted and placed in the oesophagus. The oesophageal heat exchanger was connected to a MicroTemp water heating pump (SeaBrook Medical Inc.), set at 50 litre h^{-1}, to give a temperature of 40 °C (range 38–41 °C) in the oesophageal tube. The heating was commenced before surgical incision and was maintained until the end of surgery, when the oesophageal warming device was removed. The median duration of surgery was 103 min.

The patients were premedicated with i.m. papaveretum 10–15 mg 1 h before surgery. All patients received general anaesthesia comprising thiopentone, pancuronium, nitrous oxide in oxygen and enflurane (inspired concentration 1–1.3%). Hartmann's solution was infused i.v. at room temperature and blood, if required, was transfused after being warmed to 37.0 °C.

Tympanic temperature was recorded with the MON-A-THERM (Mallinckrodt) temperature probes, calibrated in the temperature range of 25–40 °C and accurate to 0.1 °C. Skin temperatures were measured at 15 points, using the Infra-red Radiation Thermometer (Minolta Cyclops 33), obviating the need for placing temperature probes on the skin [3].

Temperature readings were taken before induction

P. Kulkarni*, M.B., B.S., F.R.C.ANAES., A. Matson, M.B., B.S., F.R.C.ANAES., F. Carli, M.D., F.R.C.ANAES. (Department of Anaesthetics); J. Bright, B.SC., J. Pearson, M.SC. (Section of Medical Statistics); Northwick Park Hospital and Clinical Research Centre, Watford Road, Harrow, Middlesex HA1 3UJ. Accepted for Publication: September 17, 1992.

*Present address, for correspondence: Department of Anaes-

TABLE I. *Median (range) core and skin temperatures and total body heat (TBH) changes,* P *values and 95% confidence limits for differences between control and treated group (95% CL). BI = Before induction; ES = end of surgery; R = 1 h in recovery*

	Control	Treated	*P*	95% CL
Core temp. (°C)				
ES–BI	−1.80 (−3.40, −0.30)	−1.30 (−2.20, −0.40)	0.09	(−1.00, 0.10)
R–ES	1.05 (−0.20, 1.70)	0.50 (−0.50, 1.40)	0.13	(−0.10, 1.10)
Mean skin temp. (°C)				
ES–BI	−1.02 (−2.13, 1.18)	0.26 (−3.38, 2.16)	0.03	(−2.03, −0.17)
R–ES	1.41 (−0.51, 3.08)	0.06 (−2.34, 1.22)	0.004	(0.23, 2.17)
TBH (kJ)				
ES–BI	−318 (−675, −114)	−219 (−613, 25)	0.34	(−247, 89)
R–ES	185 (70, 489)	69 (−95, 352)	0.02	(40, 297)

of anaesthesia, at the end of surgery but before antagonism of neuromuscular block and 1 h into recovery for both groups of patients. Other data recorded were the operating theatre temperature (median 20 °C) and the relative humidity. The mean skin temperature (MST) was calculated using the modified unweighted 15 sites formula of Hardy and DuBois [4, 5]. The 15 sites were: forehead, face, neck, nipple, mid arm, mid forearm, dorsum of hand, anterior abdomen, iliac crest, mid thigh (medial and lateral), knee, mid calf (medial and lateral) and the dorsum of the foot. Total body heat (TBH) was calculated from mean body temperature (MBT):

$$\text{MBT (°C)} = (0.66 \times \text{aural canal temp.}) + (0.34 \times \text{MST})$$

$$\text{TBH (kJ)} = \text{MBT} \times \text{body weight (kg)} \times 0.83\ \text{(specific heat)} \times 4.186$$

The changes in the core and skin temperatures and TBH during the period before induction to after surgery and 1 h after recovery were compared between the control and the treated group, using Mann–Whitney tests.

There was a significant decrease in core temperatures in both groups; however, there was no difference between the groups ($P = 0.09$). There was a decrease of 1.02 °C in the mean skin temperature during surgery in the control group; in the treated group, an increase of 0.26 °C was observed for the same period ($P = 0.03$). This was followed, in recovery, by an increase in mean skin temperature in the control group compared with the treated group ($P = 0.004$). There were similar changes in total body heat content in both groups during the study (table I).

COMMENT

We have found that the oesophageal heat exchanger was ineffective in preventing the decrease in core temperature and body heat content during hip surgery. However, measurement of surface skin temperatures at 15 sites in the treated group showed an increase in mean skin temperature at the end of surgery.

In spite of its bulk, the oesophageal warming device was easy to insert and there was no trauma to oesophageal tissue. The exact location in the oesophagus could be checked and, because of its design, rapid warming of the surrounding structures could be achieved. Nevertheless, core temperature decreased by more than 1 °C in the treated group. One possible explanation for this change may be the fact that the lower one-third of the oesophagus is less perfused than the surrounding structures. In addition, the pressure exerted by the rubber sheath on the oesophageal wall might affect heat transfer. Thus, although the device is in close proximity to large vessels, it may not be the most efficient site for transferring heat to the rest of the body. Another reason for the observed decrease in core temperature could be the low operating theatre temperature (19–20 °C in this study), leading to considerable heat loss from the periphery in the form of cutaneous heat flux. The distribution and transfer of body heat through the skin in relation to the environmental temperature plays a considerable part in temperature homeostasis.

The decrease in core temperature observed in the oesophageal heat exchanger group at the end of surgery was associated with increased mean skin temperatures, which would suggest a response to core warming and a consequent redistribution of body heat to the periphery. A similar response to core warming has been reported previously, in a similar population undergoing hip arthroplasty in a cool environment [6]. However, those patients were warmed actively by means of a heated humidifier, set at 40.0 °C, in the breathing system. Their mean skin temperature increased significantly, by 0.7 °C, while the decrease in core temperature was very small (0.3 °C). These findings would, therefore, indicate the importance of efficient and adequate core warming to attenuate radiation heat loss; this was not achieved efficiently in our study using the oesophageal heat exchanger.

ACKNOWLEDGEMENT

We thank Pennco Medical Ltd, London, for supplying the oesophageal warming devices used in this study.

REFERENCES

1. Wood MLB, Carli F. Inadvertent hypothermia in the operating theatre. Etiology, prevention and treatment. *Current Anaesthesia and Intensive Care* 1991; 2: 222–231.
2. Kristensen G, Guldager H, Gravensen H. Prevention of perioperative hypothermia in abdominal surgery. *Acta Anaesthesiologica Scandinavica* 1986; 30: 314–316.
3. Ramachandra V, Allan LG, Carli F. The Cyclops 33 radiation

thermometer: An appraisal for use in anaesthesia. *Anaesthesia* 1989; **44**: 328–331.

4. Mitchell D, Wyndham CH. Comparison of weighting formulas for calculating mean skin temperature. *Journal of Applied Physiology* 1969; **26**: 616–622.
5. Hardy JD, DuBois EF. The technic of measuring radiation and convection. *Journal of Nutrition* 1938; **15**: 461–475.
6. Ip Yam PC, Carli F. Maintenance of body temperature in elderly patients who have joint replacement surgery. A comparison between the heat and moisture exchanger and heated humidifier. *Anaesthesia* 1990; **45**: 563–565.

British Journal of Anaesthesia 1993; 70: 219–220

EFFECTS OF LORAZEPAM ON OXYGEN SATURATION BEFORE CARDIAC SURGERY

J. S. S. POLLOCK AND G. N. C. KENNY

SUMMARY

*We have studied patients presenting for coronary artery bypass surgery on two nights before surgery. Oxygen saturation during a night when the patient received no night sedation was compared with the night before surgery, when lorazepam 3–4 mg was given. There was no difference between the two nights when the total time at oxygen saturations less than 90% were compared, but the minimum oxygen saturation value when the patient received lorazepam was significantly smaller. No patient had significant sleep apnoea. (*Br. J. Anaesth. 1993; **70**: 219–220)

KEY WORDS

Hypnotics, benzodiazepines: lorazepam. Oxygen: saturation. Premedication: night sedation.

Angina and hypertension have been reported to occur in patients with sleep apnoea syndrome [1]. Patients presenting for coronary artery bypass surgery have angina and often have treated hypertension. Benzodiazepines are often prescribed, but these drugs are known to worsen pre-existing oxygen desaturation [2]. The aim of the present study was to compare the oxygen saturation and frequency of apnoea during a night when the patient received no sedation, with the night before bypass surgery when lorazepam was prescribed.

METHODS AND RESULTS

Informed consent was obtained from 17 male patients (age range 48–63 yr; weight range 64.5–83.7 kg) undergoing elective coronary bypass surgery. Patients who had significant respiratory disease were excluded. An oximeter (Biox 3700, Ohmeda) finger probe was attached to the patient before sleep and the output connected to an Atari computer, during a night when the patient received no sedation.

The oxygen saturation and heart rate were recorded to disc by a program which recorded oxygen saturation values every 3 min, unless the value decreased by more than 5% from the baseline, when data were recorded every 10 s until the patient awoke in the morning.

The patients received lorazepam 3 or 4 mg on the night before surgery and a second night's recording was obtained. The results were analysed to determine the percentage of the time spent at oxygen saturation values greater and less than 90%. The baseline oxygen saturation and the minimum oxygen saturation recorded were compared between the two nights. Data from the unsedated (normal) night and the sedated night were analysed using Student's paired *t* tests and Spearman's rank correlation test as appropriate.

Two patients were excluded from the results: one had unsatisfactory recordings caused by probe failure and the second had pulsus bigemini and a heart rate of less than 45 beat min^{-1} which gave inaccurate oxygen saturations.

Of the remaining 15 patients, six gave a history of treated hypertension and nine had a previous infarct. No patient gave a history of sleep apnoea; four patients did not snore and one patient was a severe snorer.

The oxygen saturation results (table I) were analysed to determine the percentage of time spent at oxygen saturations greater and less than 90%. During the sedation night, there was no difference in the total percentage time that the patients spent at oxygen saturation greater than 90%, compared with the non-sedated night. Two patients had oxygen saturations less than 90% for lengthy periods: one improved his oxygen saturation during the lorazepam night, while the other had smaller values. The mean minimum oxygen recorded value during the sedation night was significantly less than the non-sedated night ($P < 0.05$). Ten patients decreased their minimum value, three remained at the same value and one patient recorded a greater minimum oxygen saturation.

TABLE I. *Mean* (SD) *percentage of the total time spent at oxygen saturation* (Sp_{O_2}) *greater or less than 90% and the minimum* Sp_{O_2} *recorded.* *$P < 0.017$ *compared with normal night*

	Time (%) spent at		
	$Sp_{O_2} > 90\%$	$Sp_{O_2} < 90\%$	Min. Sp_{O_2} (%)
Normal night	95.0 (6.5)	4.9 (6.9)	87.3 (5.2)
Sedated night	93.9 (14.4)	6.0 (14.4)	83.5 (6.0)*

J. S. S. POLLOCK*, F.R.C.ANAES.; G. N. C. KENNY, B.SC.(HONS), M.D., F.R.C.ANAES.; University Department of Anaesthesia, Glasgow Royal Infirmary, 8–16 Alexandra Parade, Glasgow G31 2ER.
Accepted for Publication: September 17, 1992.

*Present address: Department of Anaesthesia, Victoria Infirmary, Langside Road, Glasgow G42 9TY.

No patient had significant sleep apnoea (defined as more than five oxygen saturation decreases, lasting 10 s or more in 1 h, the oxygen saturation decrease being 5 % or more from the patient's baseline oxygen saturation).

COMMENT

Patients who suffer hypertension have been shown to have an increase in sleep apnoea [3], while habitual snoring, a symptom of sleep apnoea, has been associated with angina, hypertension and ischaemic heart disease [1, 4]. In these patients, the ensuing oxygen desaturation from sleep apnoea may contribute to myocardial ischaemia [5]. Obstructive sleep apnoea, the most common type of sleep apnoea, has an increased frequency in males and in the age range 40–60 yr. These ages are similar to those of patients presenting for coronary artery bypass.

We found no patient with sleep apnoea, possibly because several of the patients developed angina after a myocardial infarction, rather than having a long history of progressing angina culminating in the need for coronary artery bypass. Hypertension in other patients was discovered at the time of infarction and may or may not have been present before the infarction. Coronary artery disease is multifactorial and the part that sleep apnoea plays in hypertension and angina remains to be determined.

A premedication regimen of lorazepam, morphine and droperidol in CABG patients has been found to decrease oxygen saturation [6] and to be associated with new ECG changes indicating further ischaemia in some patients. In the present study, lorazepam did not worsen the overall oxygen saturation during the sedation night, although one patient who had severe snoring, had a decreased oxygen saturation. In patients with a history of heavy snoring, this may indicate decreased oxygen saturation values and the need for added oxygen if benzodiazepines are prescribed.

In this study, the minimum oxygen saturation values were reduced significantly compared with the values recorded during the sedation night. It has been recommended that oxygen supplementation be given to cardiac patients premedicated with an opioid and this regimen may be recommended also for patients who receive benzodiazepines.

REFERENCES

1. Koskenvuo M, Kaprio J, Partinen M, Langinvainio H, Sarna S, Heikkla K. Snoring as a risk factor for angina and hypertension. *Lancet* 1985; 1: 893–895.
2. Dolly FR, Block AJ. Effect of flurazepam on sleep-disordered breathing and nocturnal desaturation in asymptomatic subjects. *American Journal of Medicine* 1982; 73: 239–243.
3. Kales A, Bixler EO, Caddieux RJ, Schneck DW, Shaw LC, Locke TW, Vela-Bueno A, Soldatos CR. Sleep apnoea in a hypertensive population. *Lancet* 1984; 2: 1005–1008.
4. Koskenvuo M, Kaprio V, Telakivi T, Partinen M, Heikkila K, Sarna S. Snoring as a risk factor for ischaemic heart disease. *British Medical Journal* 1987; **294**: 16–19.
5. Reeder MK, Muir AD, Foëx P, Goldman MD, Loh L, Smart D. Postoperative myocardial ischaemia: temporal association with nocturnal hypoxemia. *British Journal of Anaesthesia* 1991; **67**: 626–631.
6. Marjot R, Valentine S. Arterial oxygen saturation following premedication for cardiac surgery. *British Journal of Anaesthesia* 1990; **64**: 737–740.

British Journal of Anaesthesia 1993; **70**: 221–222

EFFECTS OF MIDAZOLAM ON INSULIN SECRETION FROM ISOLATED RAT PANCREATIC ISLETS OF LANGERHANS

J. P. DESBOROUGH, P. M. JONES, S. J. PERSAUD AND S. L. HOWELL

SUMMARY

Isolated, cultured rat pancreatic islets of Langerhans were incubated in medium containing glucose 2 or 20 mmol litre^{-1} and with glucose supplemented with midazolam 10, 100 or 1000 ng ml^{-1}. Glucose 20 mmol litre^{-1} with the addition of noradrenaline 10 µmol litre^{-1} was used as a control. In contrast with noradrenaline, midazolam did not inhibit glucose-induced insulin secretion. Noradrenaline 10 µmol litre^{-1} inhibited secretion to basal values in response to glucose 20 mmol litre^{-1} ($P < 0.001$). (Br. J. Anaesth. 1993; **70**: 221–222)

KEY WORDS

Hormones: insulin. Hypnotics, benzodiazepines, midazolam.

Midazolam facilitates the effect of the inhibitory neurotransmitter γ-aminobutyric acid (GABA). In a recent clinical study [1], circulating concentrations of insulin were found to be decreased significantly after induction of anaesthesia with midazolam 0.42 mg kg^{-1} over 5 min; a control group of patients received a sleep dose of thiopentone, after which serum concentrations of insulin were unchanged. Benzodiazepine receptors have been demonstrated in rat pancreatic tissue [2] and GABA has been found in both rat and human pancreatic islets [3], although at present there is no consensus on the effects of GABA agonists on the insulin secretory response [4]. It was suggested [1] that a possible cause of the decrease in serum insulin concentrations seen clinically after midazolam could be direct inhibition of insulin secretion. In this study, we have investigated the effects of midazolam on glucose-stimulated insulin secretion from isolated rat pancreatic islets *in vitro*.

METHODS AND RESULTS

Islets were isolated from Wistar rats (150–200 g) by collagenase digestion of the pancreas [5]. In some experiments, islets were cultured overnight as described [5], in RPMI 1640 medium supplemented with streptomycin 100 µg ml^{-1}, penicillin 100 u ml^{-1} and fetal calf serum (10% v/v), and maintained at 37 °C in an atmosphere of 5% carbon dioxide in air. After 24 h, the islets were harvested and washed with a bicarbonate-buffered physiological salt solution, pH 7.4, supplemented with bovine serum albumin 0.5 mg ml^{-1} and calcium chloride 2 mmol litre^{-1}. Basal insulin secretion was measured in buffers containing glucose 2 mmol litre^{-1} and secretion was stimulated by the presence of glucose 20 mmol litre^{-1}. The effects of midazolam on insulin secretion were investigated by the addition of midazolam 10, 100 and 1000 ng ml^{-1}. The effects of noradrenaline, a potent inhibitor of insulin secretion via alpha$_2$ receptors [5], were also assessed. The islets were incubated for 60 min at 37 °C, sedimented by centrifugation (9000 *g*, 15 s) and supernatant samples stored at −20 °C until assay. Insulin was measured in the samples by radioimmunoassay using guineapig anti-insulin serum, purified rat insulin as standard and ^{125}I-labelled bovine insulin. For each experiment, samples were analysed in a single assay and the intra-assay coefficient of variation was 5.2%. Results are expressed as mean (SEM); $n = 7–9$. Differences between groups were analysed by unpaired Student's *t* test and considered significant when $P < 0.05$.

In experiments using freshly isolated islets, basal insulin secretion (glucose 2 mmol litre^{-1}) per islet was 1.83 (0.49) ng h^{-1} and glucose-stimulated secretion (20 mmol litre^{-1}) per islet was 6.05 (0.74) ng h^{-1} ($P < 0.01$). Midazolam 100 and 1000 ng ml^{-1} had no effect on glucose-stimulated secretion: 4.35 (0.75) ng h^{-1} and 5.64 (0.52) ng h^{-1}, per islet, respectively. As the collagenase isolation of islets may damage islet B-cell surface receptors, islets were cultured for 24 h to allow for receptor regeneration.

TABLE I. *Mean* (SEM) *insulin secretion from cultured rat islets of Langerhans.* **$P < 0.001$ compared with glucose alone. NA = noradrenaline. Basal secretion = in response to glucose 2 mmol litre^{-1}; glucose-stimulated = in response to glucose 20 mmol litre^{-1}*

	Basal secretion (ng h^{-1} per islet) ($n = 7$)	Glucose stimulated (ng h^{-1} per islet) ($n = 9$)
Glucose alone	2.09 (0.69)	4.35 (0.52)
Midazolam (ng ml^{-1})		
10	2.53 (0.46)	4.23 (0.78)
100	2.03 (0.37)	4.38 (0.43)
1000	1.37 (0.27)	3.65 (0.35)
NA 10 µmol litre^{-1}	1.31 (0.20)	1.33 (0.13)*

J. P. DESBOROUGH, M.B., CH.B., F.R.C.ANAES., Department of Anaesthetics, Royal Postgraduate Medical School, Hammersmith Hospital, Du Cane Road, London W12 0HS. P. M. JONES, PH.D.; S. P. PERSAUD, PH.D.; S. L. HOWELL, PH.D.; Biomedical Sciences Division, Kings College, Campden Hill Road, London W8 7AH.

Accepted for Publication: September 4, 1992.

Correspondence to J.P.D.

The results of two experiments using cultured islets are shown in table I. Basal insulin secretion in the presence of glucose 2 mmol litre^{-1} was not affected significantly by midazolam or noradrenaline. Glucose-induced secretion was not altered significantly by the presence of midazolam in the incubation buffer, but the addition of noradrenaline 10 µmol litre^{-1} caused complete inhibition of glucose-induced insulin secretion ($P < 0.001$ compared with glucose 20 mmol litre^{-1} alone).

COMMENT

Although caution must be exercised in making comparisons between species and in extrapolating from *in vitro* preparations to clinical investigations, it appears unlikely that midazolam has any significant direct effect on insulin secretion, as this *in vitro* study showed no effect of any of three concentrations of midazolam on basal or glucose-induced insulin secretion from cultured islets.

Catecholamines cause marked inhibition of insulin secretion from isolated islets of Langerhans [5]. This is thought to be mediated directly via alpha-adrenergic adrenoceptors on the islet cells. In this study, we used noradrenaline 10 µmol litre^{-1} as a control for the inhibition of glucose-induced insulin secretion, to demonstrate that cell surface receptors and the appropriate intracellular signal transduction systems were present in the cultured rat islets.

The concentrations of midazolam used in this *in vitro* study were based on previous reports of values obtained clinically in patients receiving the drug as an anaesthetic for major surgery [6]. Regimens for total i.v. anaesthesia using midazolam are based upon obtaining a steady state concentration of about 300 ng ml^{-1}. Similar concentrations of midazolam have been found to provide satisfactory anaesthesia in combination with fentanyl during abdominal surgery. However, peak values after i.v. bolus injection of midazolam 0.3 mg are about 900 ng ml^{-1}, and serum concentrations of midazolam in critically ill patients with reduced organ perfusion may reach several thousand ng ml^{-1}.

Previous studies of the effects of GABA agonists on insulin secretion have had variable results [4]. To summarize: neither GABA itself or GABA agonists appear to affect insulin secretion from islets directly. Studies in the dog have shown inhibition of secretion, whereas two human studies suggest that GABA may enhance basal and glucose-stimulated insulin secretion.

As it appears that midazolam does not directly inhibit insulin secretion, alternative explanations must account for the results obtained in the previously reported clinical study using midazolam [1]. It is possible that, in some patients, extremely large serum concentrations of the benzodiazepine were produced after i.v. injection of midazolam 0.42 mg kg^{-1} over 5 min. As insulin secretion is inhibited by catecholamines, an increase in circulating concentrations of adrenaline or release of noradrenaline from sympathetic nerve endings may impair insulin release from the pancreas. Circulating concentrations of catecholamines were not measured in the clinical study [1], but indirect evidence of sympathetic activity, as shown by values of mean arterial pressure and heart rate, were not significantly different between patients who received midazolam and the control group [1]. Variations in circulating concentrations of the counter-regulatory hormones, cortisol and adrenaline, mediate metabolic changes which may have had secondary effects on insulin secretion.

In conclusion, we have demonstrated that midazolam did not directly inhibit glucose-stimulated insulin secretion from an *in vitro* rat islet preparation. In this respect, our results with midazolam were similar to those obtained using other GABA agonists and GABA itself.

REFERENCES

1. Desborough JP, Hall GM, Hart GR, Burrin J. Midazolam modifies pancreatic and anterior pituitary hormone secretion during upper abdominal surgery. *British Journal of Anaesthesia* 1991; **67**: 390–396.
2. De Souza EB, Anholt RRH, Murphy KMM, Snyder SH, Kuhar MJ. Peripheral type benzodiazepine receptors in endocrine organs. *Endocrinology* 1985; **116**: 567–573.
3. Okada Y, Taniguchi H, Shimada C. High concentration of GABA and high glutamate decarboxylase activity in rat pancreatic islets and human insulinoma. *Science* 1976; **194**: 620–622.
4. Sorensen RL, Garry DG, Brelje TC. Structural and functional considerations of GABA in islets of Langerhans. *Diabetes* 1991; **40**: 1365–1374.
5. Persaud SJ, Jones PM, Howell SL. Effects of *Bordetella pertussis* toxin on catecholamine inhibition of insulin release from intact and electrically permeabilised rat islets. *Biochemical Journal* 1989; **258**: 669–675.
6. Persson MP, Nilsson A, Hartvig P, Tamsen A. Pharmacokinetics of midazolam in total i.v. anaesthesia. *British Journal of Anaesthesia* 1987; **59**: 548–556.

British Journal of Anaesthesia 1993; **70**: 223–225

CASE REPORTS

VISUALIZATION OF EXTRADURAL BLOOD PATCH FOR POST LUMBAR PUNCTURE HEADACHE BY MAGNETIC RESONANCE IMAGING

A. G. GRIFFITHS, S. C. BEARDS, A. JACKSON AND E. L. HORSMAN

SUMMARY

We describe a case of post lumbar puncture headache treated by extradural blood patch. Magnetic resonance imaging (MRI) demonstrated a large extradural haematoma extending over four spinal segments and extending out through the neural outlet foramina. There was significant compression of the thecal sac, supporting the theory that extradural blood patch causes tamponade at the site of dural puncture. The spread of clot was predominantly upwards from the injection site and subarachnoid extension of blood was also demonstrated. (Br. J. Anaesth. 1993; **70**: 223–225)

KEY WORDS

Anaesthetic techniques: extradural. Complications: post lumbar puncture headache. Measurement techniques: magnetic resonance imaging

CASE REPORT

A 35-yr-old woman (gravida 2, para 1, weight 78 kg, height 164 cm) was admitted in established labour. One hour after admission, artificial rupture of membranes was performed. Extradural anaesthesia was requested and an initial attempt at extradural puncture was made at the L2–3 interspace, using loss of resistance to air with the patient in the sitting position. During insertion of the needle, the patient moved suddenly and fluid was seen to drip through the Tuohy needle. The needle was resited at the L3–4 interspace without difficulty and an extradural catheter was inserted to a distance 3 cm in the extradural space. After negative aspiration, a test dose of 2% lignocaine 3 ml was injected through the catheter. This resulted unexpectedly in rapid onset of a bilateral sensory block to T7. Additional local anaesthetic agent was not administered and the catheter was removed immediately after delivery. The patient underwent uneventful vaginal delivery of a 4.04-kg male 80 min after insertion of the extradural catheter.

Twelve hours after delivery, the patient developed a severe postural headache radiating to the neck and a diagnosis of spinal headache was made. A 24-h trial of conservative treatment was unsuccessful and an extradural blood patch was performed 36 h after delivery.

After obtaining local Ethics Committee approval and informed consent from the patient, we performed an initial MRI scan of the lumbar spine. MRI was performed on a 0.5 Tesla GE MAX Scanner. Contiguous, 5-mm thick parasagittal T1 weighted gradient echo (GE 500/14) images were obtained throughout the lumbar spine to include the neural exit foramina on each side. A series of 5-mm axial T1 weighted images (GE 550/14) were also obtained, extending from T11 to the sacrum. All initial scans were normal (fig. 1).

MRI was followed by an uneventful extradural puncture at the L1–2 interspace with the patient in the sitting position, using loss of resistance to air. After injection of 18 ml of autologous venous blood into the extradural space, the patient experienced immediate relief of headache.

The MRI scan was repeated 30 min after injection of the blood patch, using the same imaging routines

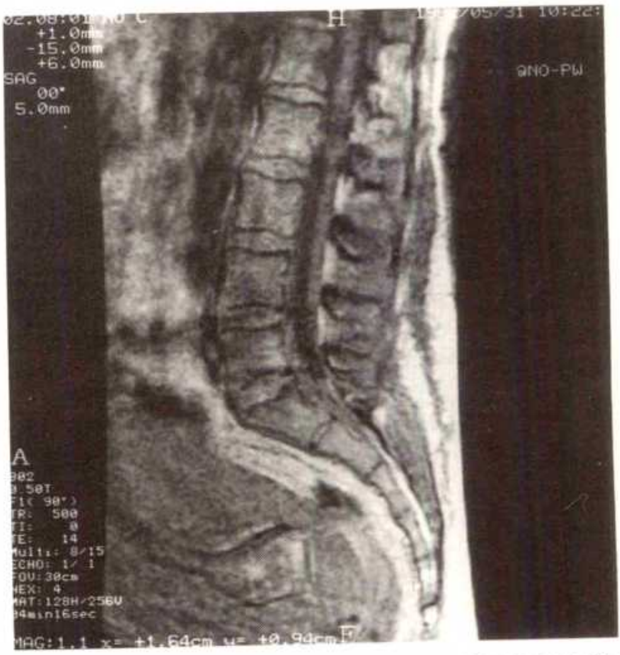


FIG. 1. Midline T1 weighted sagittal section (GE 500/14/90) showing normal appearances before blood patch.

AMANDA G. GRIFFITHS, M.B., CH.B., F.R.C.ANAES., SUSAN C. BEARDS*, B.SC., M.B., CH.B., F.R.C.ANAES., E. L. HORSMAN, M.B., CH.B., F.R.C.ANAES. (Department of Anaesthesia); ALAN JACKSON, PH.D., M.R.C.P., F.R.C.P. (Department of Neuroradiology); Manchester Royal Infirmary, Oxford Road, Manchester M13 9WL.
Accepted for Publication: July 30, 1992.

* Address for correspondence: 24, Greenwood Drive, Wilmslow, Cheshire SK9 2RW.

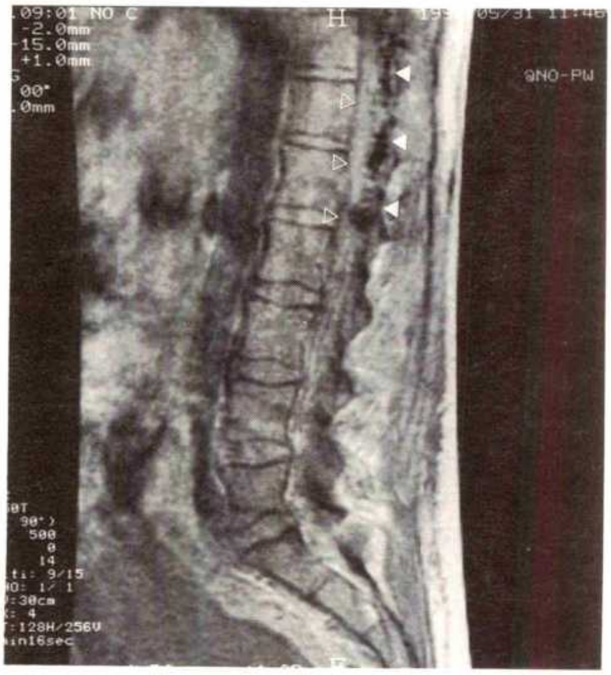


FIG. 2. Midline sagittal section (GE 500/14/90) after blood patch showing extensive blood clot (arrow heads) displacing the conus medullaris and cauda equina (open arrow heads) anteriorly.

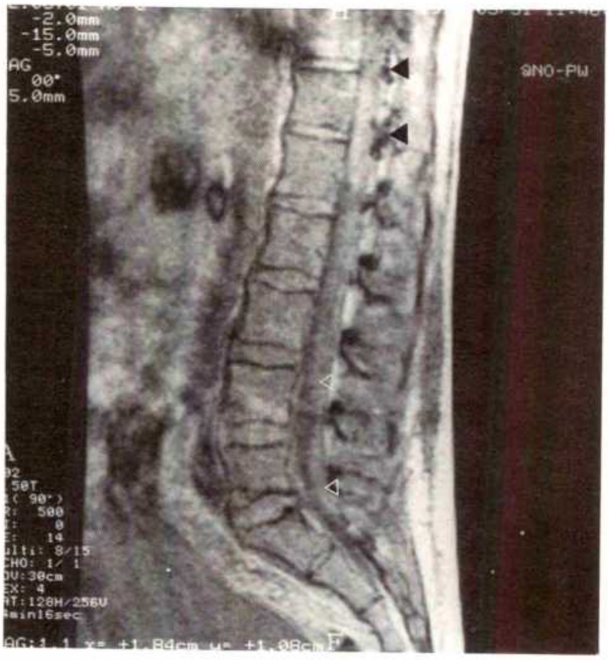


FIG. 3. Parasagittal section showing the distribution of developing clot (black areas) at the levels of the intervertebral discs (black arrowheads). Caudal spread of more mature haematoma (grey areas) is also demonstrated (open arrowheads).

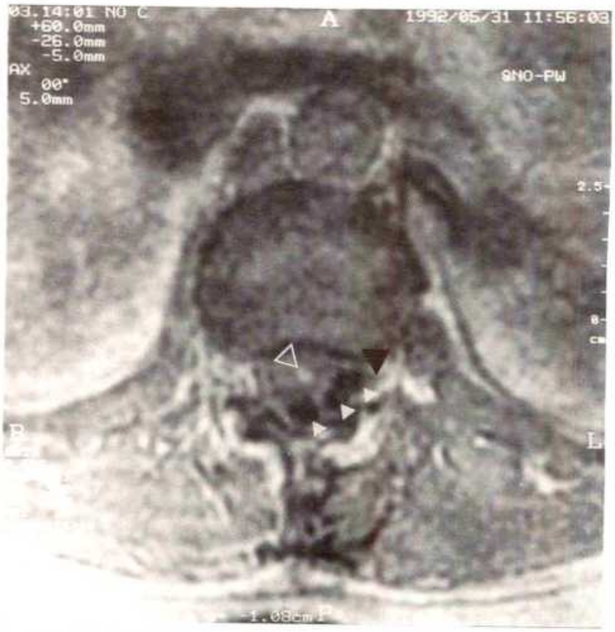


FIG. 4. Axial image at the level of the T12–L1 intervertebral disc showing clot (small arrowheads) displacing the thecal sac, conus medullaris (open arrowhead) and left D12 nerve root (black arrowhead) within the exit foramen.

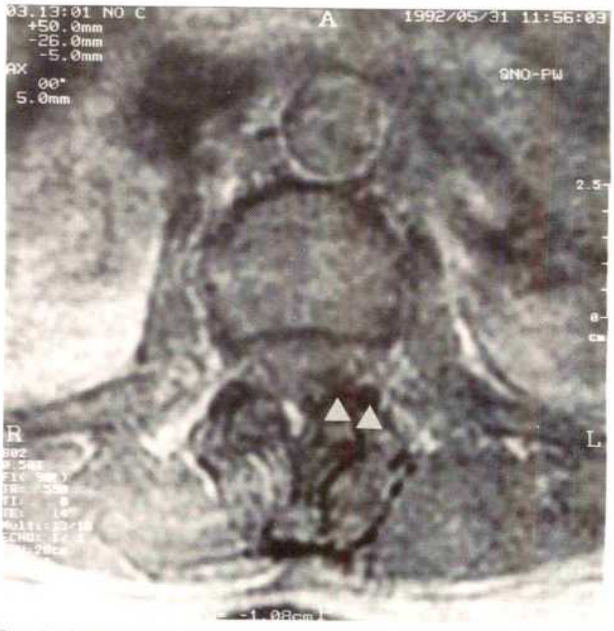


FIG. 5. Axial image at the level of the L1–2 disc showing high signal from CSF, indicating subarachnoid spread of blood and extension of clot (arrowheads) through the intervertebral foramen.

described above. Parasagittal images (figs 2, 3) demonstrated a sizeable blood clot in the posterior extradural space. This clot extended upwards from the injection site to the T11–12 intervertebral space and down one interspace to the L2–3 level. The clot was largest at the levels of the intervertebral discs, where the sagittal diameter of the spinal canal is greatest (figs 2, 3). The clot caused considerable mass effect, compressing the thecal sac and displacing the conus medullaris and the upper cauda equina anteriorly and to the right (fig. 4). Axial images at T11–12, T12–L1 and L1–L2 (fig. 5) also demonstrated clot extending out through the lateral recess into the neural exit foramina on the right side, with anterior displacement of the exiting nerve roots.

In addition to the focal clot at the injection site, a thin irregular layer of more mature clot was present, extending down the posterior aspect of the thecal sac into the upper part of the sacral recess (fig. 3) and anteriorly into the anterior extradural space.

There was considerable change in the intensity of the CSF within the subarachnoid space after the blood patch. CSF normally appears black on T1 weighted images (fig. 1); however, after blood

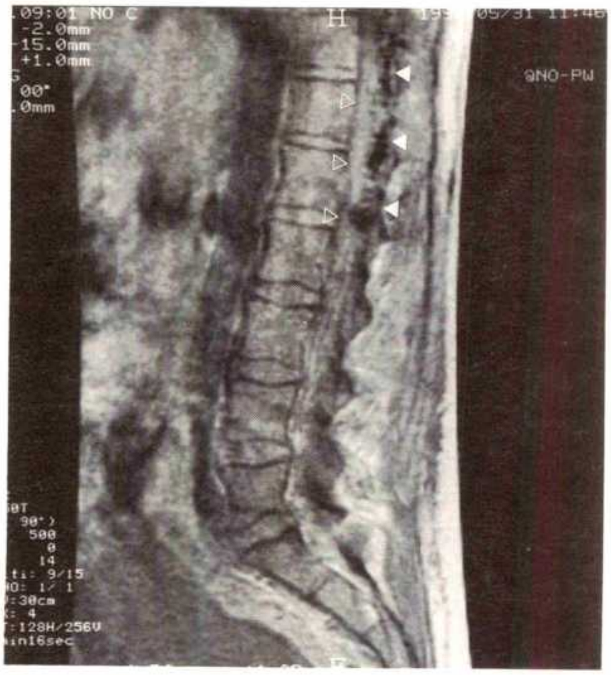


FIG. 2. Midline sagittal section (GE 500/14/90) after blood patch showing extensive blood clot (arrow heads) displacing the conus medullaris and cauda equina (open arrow heads) anteriorly.

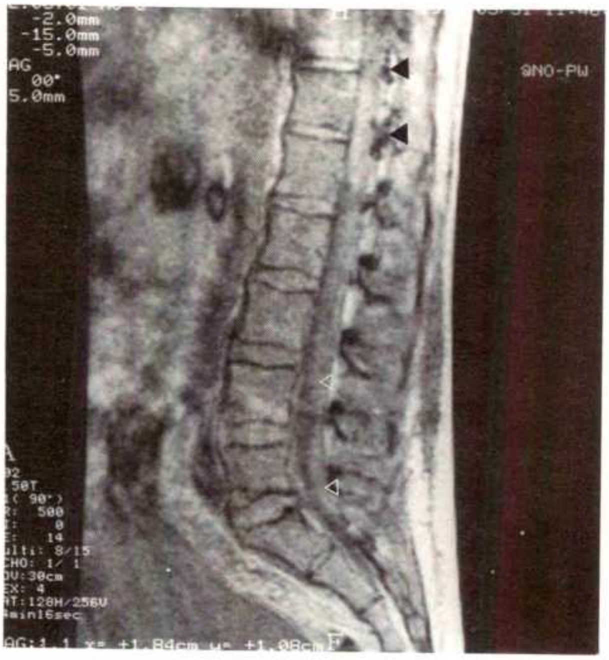


FIG. 3. Parasagittal section showing the distribution of developing clot (black areas) at the levels of the intervertebral discs (black arrowheads). Caudal spread of more mature haematoma (grey areas) is also demonstrated (open arrowheads).

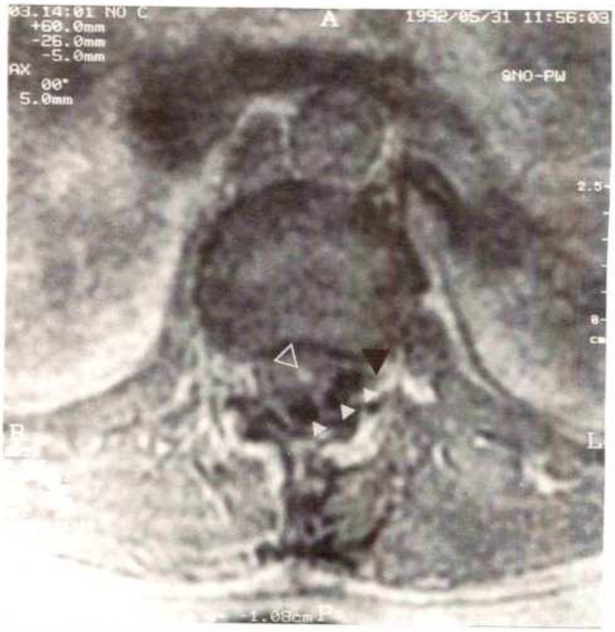


FIG. 4. Axial image at the level of the T12–L1 intervertebral disc showing clot (small arrowheads) displacing the thecal sac, conus medullaris (open arrowhead) and left D12 nerve root (black arrowhead) within the exit foramen.

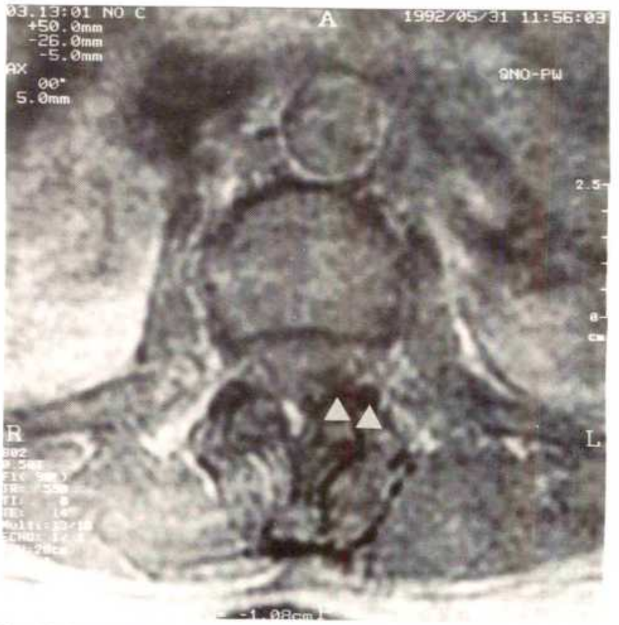


FIG. 5. Axial image at the level of the L1–2 disc showing high signal from CSF, indicating subarachnoid spread of blood and extension of clot (arrowheads) through the intervertebral foramen.

described above. Parasagittal images (figs 2, 3) demonstrated a sizeable blood clot in the posterior extradural space. This clot extended upwards from the injection site to the T11–12 intervertebral space and down one interspace to the L2–3 level. The clot was largest at the levels of the intervertebral discs, where the sagittal diameter of the spinal canal is greatest (figs 2, 3). The clot caused considerable mass effect, compressing the thecal sac and displacing the conus medullaris and the upper cauda equina anteriorly and to the right (fig. 4). Axial images at T11–12, T12–L1 and L1–L2 (fig. 5) also demonstrated clot extending out through the lateral recess into the neural exit foramina on the right side, with anterior displacement of the exiting nerve roots.

In addition to the focal clot at the injection site, a thin irregular layer of more mature clot was present, extending down the posterior aspect of the thecal sac into the upper part of the sacral recess (fig. 3) and anteriorly into the anterior extradural space.

There was considerable change in the intensity of the CSF within the subarachnoid space after the blood patch. CSF normally appears black on T1 weighted images (fig. 1); however, after blood

British Journal of Anaesthesia 1993; **70**: 226–227

MUSCULAR PARALYSIS AND VENTILATORY FAILURE CAUSED BY HYPERKALAEMIA

S. J. FREEMAN AND A. D. FALE

SUMMARY

We report the history of a diabetic man presenting with hyperkalaemia and rapidly progressing muscular paralysis with severe respiratory embarrassment. His symptoms resolved rapidly with reduction of the serum potassium concentration. Similar cases have been reported previously but this is a problem that few will have encountered and is a diagnosis which should not be overlooked before artificial ventilation is commenced. (Br. J. Anaesth. 1993; **70**: 226–227)

KEY WORDS

Complications: hyperkalaemia. Complications: paralysis. Ventilation: failure.

CASE REPORT

A 75-yr-old man was admitted with a short history of progressive ascending muscular weakness. He had a history of maturity onset diabetes mellitus, severe peripheral vascular disease with a right femoro–popliteal bypass and benign prostatic hypertrophy for which he had undergone TURP 2 months before admission, when his serum creatinine concentration was normal (98 μmol litre^{-1}).

His usual drug treatment was glibenclamide 5 mg twice daily and metformin 1 g twice daily. One week before admission, he was prescribed amiloride–hydrochlorothiazide (Moduretic) tablets one daily for peripheral oedema.

Thirty hours before admission he had noticed difficulty getting up from a chair, which had progressed rapidly to global muscle weakness. He had not noticed any sensory symptoms or sphincter disturbance and his history gave no suggestion of a recent viral illness.

On examination, he had profound muscle weakness of arms and legs (proximal muscles MRC grade 1/5; distal muscles MRC grade 0/5), together with difficulty talking and breathing. His peak ventilatory flow rate was 70 litre min^{-1}. There was marked muscular fasciculation in the arms and legs, reflexes were depressed and plantar responses absent. He had a "stocking" loss of sensation to below the knee, mild background diabetic retinopathy, but no cranial nerve abnormalities.

A presumptive diagnosis of acute postinfective polyneuritis was made and he was transferred to the ICU for tracheal intubation and mechanical ventilation of the lungs.

Investigations

ECG showed broad QRS complexes with peaked T waves, biochemistry showed serum concentrations of sodium 127 mmol litre^{-1}, potassium 10.2 mmol litre^{-1}, chloride 101 mmol litre^{-1}, bicarbonate 17 mmol litre^{-1}, urea 18.6 mmol litre^{-1}, creatinine 207 μmol litre^{-1}, glucose 22.0 mmol litre^{-1}. Arterial blood-gas analysis revealed pH 7.29, $P\text{CO}_2$ 4.4 kPa, $P\text{O}_2$ 13.6 kPa, base excess −9 mmol litre^{-1}. CSF pressure was 15 cm H_2O, protein 166 mg litre^{-1} (ref. 155–450), glucose 8.6 mmol litre^{-1}, WBC $< 1 \times 10^9$ litre^{-1}.

Treatment and progress

There was a dramatic response to treatment with i.v. calcium gluconate, an insulin and glucose infusion and i.v. sodium bicarbonate. Within 20 min he was able to lift both hands above his head and his peak ventilatory flow rate had increased to 350 litre min^{-1}. Treatment was continued with an insulin–glucose infusion, oral calcium resonium and fludrocortisone which was withdrawn after 12 days. His serum potassium concentration fluctuated over the next 36 h mirroring changes in his peak expiratory flow rate, but then settled within the normal range. He was discharged and, at follow up 10 days later, was well, with normal serum electrolyte and creatinine concentrations. Ultrasound showed normal kidneys with no evidence of obstruction. He had normal liver function tests and serum calcium concentration and a normal response to a short synacthen test.

DISCUSSION

Both hypo- and hyperkalaemia can produce a clinical picture of flaccid muscular paralysis very similar to that of acute postinfective polyneuropathy (Guillain–Barré syndrome) and the importance of measuring the serum potassium concentration and recording an ECG early in the investigation of suspected acute postinfective polyneuropathy has been emphasized [1, 2]. In our patient, rapid recovery of muscle power after emergency treatment of

---

S. J. FREEMAN*, M.B., B.S., M.R.C.P. (Department of Medicine); A. D. FALE, M.B., CH.B. (Department of Anaesthetics); Southmead Hospital, Southmead Road, Bristol BS10 5NB. Accepted for Publication: September 9, 1992.

*Address for correspondence: Department of Radiodiagnosis, Bristol Royal Infirmary, Bristol BS2 8HW.

the hyperkalaemia, combined with normal CSF confirmed that hyperkalaemia was the cause of his paralysis.

Although cardiac arrhythmias are the usual cause of death in severe hyperkalaemia, muscular weakness may be the predominant manifestation, with ventilatory failure a potentially lethal complication, as in our patient, and occasionally artificial ventilation may be needed [3]. The use of suxamethonium as a rapidly acting neuromuscular blocker is associated with an increase in serum potassium concentration [4]; this increase may precipitate arrhythmias.

The dangers of using potassium-sparing diuretics in elderly patients, who may have some degree of renal impairment despite normal serum creatinine concentrations, are well known. Hyperkalaemia after treatment with amiloride–hydrochlorothiazide combinations has been reported previously [5]. In our patient, the period of hyperkalaemia correlated well with the duration of action of amiloride, started 1 week before presentation, and emphasizes the importance of early biochemical monitoring after starting treatment with a potassium-sparing diuretic in the elderly.

REFERENCES

1. Udezue EO, Harrold BP. Hyperkalaemic paralysis due to spironolactone. *Postgraduate Medical Journal* 1980; **56**: 254–255.
2. Livingstone IR, Cumming WJK. Hyperkalaemic paralysis resembling Guillain–Barré syndrome. *Lancet* 1979; **2**: 963–964.
3. Barker GL. Hyperkalaemia presenting as ventilatory failure. *Anaesthesia* 1980; **35**: 885–886.
4. Davies DM. *Textbook Of Adverse Drug Reactions*, 4th Edn. Oxford: Oxford Medical Publications, 1991; 410–411.
5. Jaffey L, Martin A. Malignant hyperkalaemia after amiloride/hydrochlorothiazide treatment. *Lancet* 1981; **1**: 1272.

British Journal of Anaesthesia 1993; **70**: 228–234

HISTORY

JOHN HENRY HILL LEWELLIN: THE FIRST ETHERIST IN GLASGOW

A. G. MACDONALD

SUMMARY

John Henry Hill Lewellin, a surgeon–dentist, was the first to administer ether in Glasgow, on January 4, 1847. He was born in Calcutta, trained at St Bartholomew's Hospital, qualified M.R.C.S. in London in 1842, and studied in Paris and Heidelberg, before moving to Glasgow in December 1845. He remained there for about 18 months, advertising his dental practice in a high profile manner and, when the time came, he publicized his experience with ether in the local press in an exemplary way. He disappeared from Glasgow in June 1847, and reappeared in Australia 5 years later, practising as a dentist initially, and later as a general medical practitioner in Melbourne until his retirement in 1883. He died in 1886. (Br. J. Anaesth. 1993; **70**: 228–234)

KEY WORDS
History: diethyl ether.

William Morton's historic administration of ether to Gilbert Abbot on October 16, 1846 in the Ether Dome of the Massachussett's General Hospital in Boston preceded the first administration in Britain by 9 weeks. The manner by which the news travelled from Boston to London, and independently from Boston to Dumfries, is well documented [1, 2]. James Robinson and Francis Boott administered ether to Miss Lonsdale for the removal of a firmly fixed molar tooth on Saturday, December 19, 1846 in Boott's house at 42 Gower Street, London and on the same day, in the Dumfries and Galloway Royal Infirmary, Dr William Scott operated on a patient who was under the effect of ether, having learned of the discovery from Dr Fraser, the ship's doctor on the "Acadia". There are few details about the Dumfries case, as the relevant hospital records are missing and, indeed, there almost seems to have been a cover-up over the episode, making one wonder if the administration of ether in that case went badly.

From London to Scotland

During the subsequent 2 weeks, the news of the discovery of ether also reached Scotland by private correspondence and by the daily newspapers. Robert Liston, the Scottish surgeon who had performed the first surgical procedure under ether in England at the University College Hospital, London, on Monday December 21, had corresponded with James Millar, Professor of Surgery in Edinburgh, and this resulted in the first use of ether in Edinburgh taking place in the Royal Infirmary on Saturday January 9, 1847 [3], when Dr James Duncan performed a thigh amputation on a young man who had been involved in a railway accident [4].

First use of ether in Glasgow Royal Infirmary

The first use of ether in Glasgow was thought to have taken place at The Royal Infirmary towards the end of January 1847, when Professor James Lawrie was reported to have performed several operations on patients who were under ether, although no exact dates or details are given [5]. It is probable that this initial use of ether in Glasgow took place on January 27, and was witnessed by Benjamin Ward Richardson, who was a medical student at the time, having begun his studies at Anderson's College in 1845. In his memoirs, published many years later [6], he describes the occasion vividly. He records that a Dr Fleming gave the ether vapour "from a sponge surrounded by a towel", and that Professor Andrew Buchanan did the operation, in the presence of Professor James Lawrie and Professor Moses Buchanan, Professor of Anatomy. This trial of ether was entirely successful, and ether administration soon became accepted in Glasgow. Unfortunately, no dates are recorded in these memoirs. Four further operations were performed under ether on Wednesday February 10, and were described in detail in the local press [7].

The discovery of Lewellin

All the newspaper articles relating to the introduction of ether at Glasgow Royal Infirmary had appeared in the *Glasgow Herald*. There were, however, seven daily newspapers in Glasgow in 1847, although only the *Herald* has survived. They were mostly four-page broadsheets, published twice or three times weekly. Articles printed in one newspaper often appeared in the others a few days later. This also applied to articles from the national newspapers, which were occasionally reprinted in full. For some strange reason, the *Herald* failed to

---

ALAN G. MACDONALD, M.B., CH.B., F.R.C.ANAES., M.R.C.P.GLASG., Department of Anaesthesia, Victoria Infirmary, Glasgow G42 9TY. Accepted for Publication: August 5, 1992.

copy the reports which had appeared in the *Glasgow Courier* and the *Glasgow Argus*, announcing the earlier use of ether in Glasgow.

The first that Glasgow readers knew of the discovery of ether was the report of the *Glasgow Courier* of January 1, 1847 [8], which contained the entire reprint of the famous article from the *Medical Times*, headed "Surgical Operations without Pain", which began: "We have been informed that two operations were performed by Mr Liston at University College Hospital on Saturday last...".

On January 5 [9], the *Courier* published an extract of Dr Bigelow's publication in the *Boston Medical and Surgical Journal*, which had appeared in the *Morning Chronicle* a few days before, describing in detail his experiences with 10 patients given ether. This long article provides enough information to enable anyone to go away and administer ether himself, and yet it was several weeks before Dr Lawrie used it in the Glasgow Royal Infirmary.

The *Glasgow Argus* of January 11 [10], under the heading "New Discovery in Surgery", printed an article from *Punch*, in which the writer caricatures the new miracle: "a man may have his legs cut from under him without his knowing it,...while the drawing of teeth becomes an agreeable excitement, which is so delightful that a boy having been mulcted of a molar clamoured loudly to have another extracted". This article, too, might have stimulated Glasgow surgeons to try ether, but it was another 2 weeks before they did so.

The *Herald* of January 15 [11] described Dr Duncan's first use of ether in Edinburgh—another prompt, which again had no immediate effect.

The *Courier* of Saturday January 16 [12] produced an unexpected discovery. Under the heading "Dental Surgery", an article described the use of ether by a Mr Lewellin, a Glasgow dentist, on a 23-yr-old man for the extraction of an upper molar. It is an impressive description of the procedure, revealing a scientific approach to the administration of this new agent. It describes how the inhalation continued for 2 min, being complicated slightly by the patient swallowing at one stage instead of inhaling, how the heart rate increased from 64 to 80 beat min^{-1}, and how the face became slightly flushed. It also comments that "not the least attempt at coughing as observed in the American experiment" took place. Presumably Mr Lewellin had read Bigelow's article. He also says how the tooth, of a particularly bad shape and in a difficult locality, was removed without pain. He finished by inviting anyone to come to witness the new technique.

Twelve days later, on January 28 [13], again in the *Courier*, another communication from Lewellin appeared, written two days earlier. This was a letter to the Editor, under the heading "Use of Ether in Dental Operations". It referred to a notice in the *Courier* of January 26, which apparently had stated that ether had first been used in Scotland on January 5. Lewellin made it quite clear that he had used ether one day earlier, on January 4. He added that the equipment used was similar in principle to that used in London (so he must have had knowledge of Squires' inhaler), and that the administration was witnessed "by several gentlemen, medical and scientific, as well as friends of the patient, and it was at their instigation that the case was brought before the public".

Lewellin demonstrated in this article an impressive awareness of many of the finer points of administering ether. He urged caution in not using the agent in all cases, he warned about the dangers of leaving it exposed to air and light, and he described how its toxic metabolites might injure the texture of the lungs.

He finished "I merely state these facts knowing that ether will and must become general in dental surgery for which it is peculiarly applicable, and as the greater number of dentists are not properly qualified medical practitioners, and consequently ignorant of the circumstances. With many apologies for having trespassed so far on your space, I am sir, Your obedient Servant, J. W. H. Lewellin, MRCSS, 86 West Regent Street, 26th January 1847".

This was a confidently written letter, composed in an educated and authoritative style. No doubt, his inference that most of his colleagues were less well qualified than he was would not have endeared him to many.

The M.R.C.S.S. did not appear in the lists of recognized qualifications, but was almost certainly a Membership of a Royal College (see later).

Buchanan's unsuccessful claim

The *Courier* of January 26 [14], which Lewellin had referred to, revealed an obscure paragraph, easily missed, and under a misleading heading. This stated that Mr Buchanan, another Glasgow dentist, "has introduced the vapour of ether in his practice", and that he was "the first to employ this powerful new agent in Scotland, having used it on the 5th inst". It also mentions that the apparatus used on this occasion was a bent glass tube. This piece of equipment was almost certainly the apparatus devised in December 1846 by George Buchanan of Glasgow, a cousin of this dentist, who later became Professor of Clinical Surgery in Glasgow. It is slightly confusing that both cousins had the same name, but, in his article published 51 years later [15], George Buchanan recounts how his dentist cousin had received a letter on December 22 1846 from a friend in London who had witnessed Liston's first operation under ether the day before. That same evening, he and his cousin, in the presence of his father, had experimented with ether at their home, using the bent glass tube with a bulb in the middle. There can be little doubt that this experiment must have been the first self-administration of ether in Scotland. It is remarkable also to think that, in those days, a letter posted in London on December 21 could have reached Glasgow the following day.

There is no further correspondence after Lewellin's second letter, so Buchanan must have conceded victory to Lewellin. One cannot help feeling sympathy for Buchanan, as the *Argus* of January 21 [16]—7 days before Lewellin's first announcement in the *Courier*—revealed that Buchanan actually advertised his "ETHER INHALER, similar to what has been recently used in London by

Robert Liston, Esq. and others with such eminent success. By this process the most painful operations may be performed without inconvenience to the Patient". This was therefore in print 5 days before his claim to be the first etherist in Scotland. Buchanan does not state in his advertisement that he had *actually* used the inhaler himself, although he clearly *had* done so on January 5. Nevertheless, he gets the credit of being the first to advertise the use of ether in Glasgow.

How did Lewellin hear of the discovery of ether?

The detailed account of Bigelow's experiences of ether appeared in the *Courier* on January 5, the day after Lewellin's first administration. So he must have heard about ether from another source, perhaps directly from Buchanan, or from someone in Edinburgh who knew of Liston's letter to Millar. He may even have received a personal letter from one of his London colleagues who knew of the discovery.

Another source of information was the medical journals. The first issue of the *Lancet* of 1847 was published on Friday January 1, and would have been despatched a day or two earlier. That issue contained three letters from Dr Boott to the Editor [17]. The first was a covering letter with a copy of Bigelow's personal communication to him, relating in detail his experiences with ether. The second described Robinson's extraction of Miss Lonsdale's tooth in his presence, and the third was another covering letter enclosing a letter from Liston, recounting his first two successful administrations of ether, and thanking Boott for having given him such early information of the discovery. These articles provide full details of the apparatus used and the technique of administration of ether. If Lewellin was a subscriber to the *Lancet*, he might have received this issue on or before Saturday 2, in time to study it, and to prepare for his first use of ether on Monday 4.

Lewellin advertises his use of ether

The *Glasgow Argus* of February 1, 1847 [18], only three days after Lewellin's letter claiming to be the first etherist in Scotland, contained an advertisement headed "Mr LEWELLIN, Member of the Royal College of Surgeons, London, Member of the Royal Parisian Medical Society, Surgeon Dentist". This was a more substantial announcement than Buchanan's, and informed the reader that he had devised a new and better apparatus for the administration of ether, and that he was able to regulate the dose to suit each individual. It concluded "Advice *Gratis to the Poor* from 9 to 10 every Morning except Sunday". This advertisement appeared in the *Argus* every Monday for 6 weeks, and was then replaced on April 11 [19] by an even larger one, which appeared every 2 weeks until June 21 [20]. After this date, no further evidence of Lewellin's existence in Glasgow has been found. His Membership of the Royal Parisian Medical Society is discussed later.

Lewellin's ostentatious advertising stimulated some of his dental colleagues to do likewise. One sounded reluctant at being pressurized into this: "Mr Greig... has been advised to take this mode of acquainting his Friends, that he, among others, has in several cases successfully employed the ETHER INHALER under operations" [21]. One can imagine how Lewellin's style of practice may not have pleased his rivals.

Lewellin's earlier advertising

A further search of the Glasgow newspapers of 1845 and 1846 revealed that Lewellin had begun advertising his dental practice long before ether came on the scene. His first advertisement appeared in the *Herald* on December 15 1845 [22]. It indicated that he had "lately arrived from Paris", having studied there, in some principal German Universities, and in London.

In another column of the same page of that issue of the *Herald*, there was another advertisement, headed "Avis aux Etrangers", which, in immaculate French, advised its readers that Mr Lewellin had recently arrived from Paris, where he had, for a long time, been attending courses run by its most distinguished Professors.

There was still more to come. In a third column of the same page of that now historic issue of the *Herald*, there appeared yet another advertisement, which began, "Herr Lewellin, MRCSL, Zahnarzt...", and, in very accomplished but formal German, drew attention to his years of studies in Germany and France, and to his familiarity with foreign and English methods of treatment, and declared his confidence "that he will be able to serve a most distinguished clientele always to their utmost satisfaction".

This behaviour of Lewellin was quite extraordinary, not only because of the multi-linguistic advertising used, which was surprising enough, but also in the conspicuous and high profile manner in which it was presented. Lewellin seemed intent on attracting an up-market clientele to his new practice. He may have expected there to be a growing French and German speaking population in the business and professional community of Glasgow at the time, as trading links with the mainland of Europe and the Baltic were developing fast. Glasgow was, after all, the "Second City of the Empire". However, it was unusual for dentists in Glasgow to indulge in advertising, and it is apposite to note that Lewellin's advertisements appear amongst those for Furniture Sales, Winter Hosiery, Railway Notices, Pig Iron Sales and School Holiday Dates. His advertisements continued to appear regularly throughout the next year, up to the time that he used ether.

The Royal Parisian Medical Society

The Parisian Medical Society was founded in November 1837, mainly for the benefit of British and American doctors who had come to Paris to complete their medical training. The 18 founder members were almost all members of the Royal Medical Society of Edinburgh.

An address, delivered by the Vice-President of the Society in April 1841, summarized its history, and re-affirmed its aims [23]. It stated "A visit to the Parisian University is now considered the necessary completion of a sound professional education". It is clear that one of the Society's aims was to co-ordinate the training of doctors from overseas. The membership in 1841 is recorded as being nearly 300—clearly a flourishing concern—and it was into this Society that Lewellin was presumably accepted a few years later. By that time it had become the Royal Parisian Medical Society. No records of its Proceedings have been traced, and it is likely that it was incorporated into another larger Association. It is not known therefore what part, if any, Lewellin played in its affairs, but he clearly thought it a prestigious enough Society to declare his membership of it when he began advertising his services in Glasgow a few years later.

Lewellin in Glasgow

The *Glasgow Postal Directories* of 1846 and 1847 listed Lewellin as Surgeon Dentist, 86 West Regent Street, and in 1847 his name was included in the list of 13 Dentists, all of whom resided within a few blocks of each other. Lewellin did not appear in earlier or later Directories, so it seems that he was based in Glasgow for only 2 years. The *Annual Census* lists of 1841 and 1851 for both Glasgow and London did not include Lewellin.

It seemed likely that Lewellin would have involved himself in the local dental and medical circles of the time. However, there was no Glasgow Dental Society in 1847, and the Glasgow Dental Hospital was not opened until 1879. His name did not appear in the Minutes of any of the Medical Societies of the time, the Royal Medico-Chirurgical Society of Glasgow, founded in 1814, or the Glasgow Southern Medical Society, founded in 1844. The records of the Glasgow Trades House, to which Barbers and Surgeons were affiliated, made no mention of Lewellin.

Lewellin's residence in Glasgow

Lewellin was showing considerable drive and determination in his quest to build up his dental practice in Glasgow. His residence in Glasgow was in the "New Town", that part of the city extending up Blythswood Hill from Buchanan Street, a prosperous and vibrant community, "on a very splendid scale, bearing comparison with those of any city in the Empire" [24]. West Regent Street was a new terrace of houses built in the 1830s, and No. 86 was a three-storey house on the corner of Hope Street. The houses were renumbered in 1920, but there is no doubt that Lewellin lived and practised in the building now occupied by the Yorkshire Building Society.

The search for Lewellin's origins

The very first *Medical Directory*, published in 1845, reveals "Lewellin, John Henry Hill, S1842, East Indies". The initials do not correspond with those in the *Courier*, which were incorrect. The possibility of Lewellin being related in some way to Henry Hill Hickman, is an enthralling thought, but as Hickman died in 1830, and as Lewellin's age was not yet known, it is pure speculation to imagine that they might be cousins. "S 1842" signified Membership of the Royal College of Surgeons of London, 1842. "MRCSS" in the *Courier* should have read "MRCSL": Lewellin's handwriting had been misread.

The *List of Fellows and Members of the Royal College of Surgeons in London* of 1848 records Lewellin as having passed his examination on April 8, 1842, and in the Examinations Register for that day, his name appears, showing his origin as East Indies, and his exam fee of £21 which, in the currency of the day, was 20 guineas.

An obscure section in the *Medical Directory* of 1872, under "Practitioners Resident Abroad with British Qualifications", listed "Lewellin, John Henry Hill, Prahran, Victoria, Australia, MRCS, England, 1842".

In 1874, his listing included the information that he had trained in St Bartholomew's Hospital, London, and also Paris and Heidelberg. It also recorded that he was a Justice of the Peace, and Vaccination Officer of Gardiner and Caulfield, which were Districts of Melbourne. He was appointed magistrate for the Colony of Victoria in 1868 [25]. He must have been resident for some years and have been held in high esteem to have gained these appointments.

In 1878, the Directory added "South. Rifles". Lewellin was appointed Assistant-Surgeon to the Southern Rifles with the relative rank of Lieutenant in January 1864, and was posted to the Prahran and South Yarra Corps [26]. He was promoted Captain in 1867 [27], and by 1878 he had gained the rank of Major [28].

In 1882, another Lewellin was listed: Augustus John Richard Lewellin, Prahran, Victoria, MB 1873, LKQCP, Ireland. This was Lewellin's son, who had almost certainly joined the family practice.

In 1883, the father's name disappeared, but the son's continued. No Obituary appeared in the Lists of Deaths which were, until 1914, included in these *Medical Directories*.

St Bartholomew's

The Students' Register for those studying at St Bartholomew's Hospital in the academic year 1842–43 shows Lewellin's signature, denoting his acceptance of the terms, conditions and rules of the Medical School. It did not record how long he attended, but it did provide two addresses, 40 Gibson Street, Islington, and Fort William, Calcutta. The former was almost certainly his lodgings during his time at St Bartholomew's, and the latter his home origins in the East Indies.

Fort William was the name given to the Army garrison on the banks of the River Hooghli (sometimes now spelt Hugli) in Calcutta. The Old Fort was built in the late 17th Century to protect the English traders from attack from the Nawab of Bengal [29]. The Fort was rebuilt in 1781, and became a training ground for British troops. It was likely that Lewellin's family was based in this garrison.

Lewellin's family

The *Ecclesiastical Returns of the Fort William Garrison*, of 1819, recorded the birth of John Henry

Hill Lewellin on September 18, 1818, and his baptism on May 24 1819 by John Young, garrison Chaplain. Lewellin's father was recorded as Lieutenant Henry Lewellin, of His Majesty's 24th Light Dragoons, and his mother as Anne Eliza.

There is a mystery concerning Anne Eliza. In the Schedule recording John Henry Hill's death [30], his mother was named as "Eliza Anne Lewellin, m.n. (maiden name) Farquhar or Farquharson". This conflicts with the records of her first marriage at Cawnpore, to William Lambert, in which she was named as Anne Eliza Smith, Spinster [31]. No information has yet emerged to resolve this discrepancy, but if her maiden name really was Farquhar or Farquharson, both Scottish names, this might provide a family reason for Lewellin coming to Scotland in 1845. Perhaps she gave an assumed name "Smith" to the Registrar in Cawnpore.

Lewellin in Australia

Lewellin arrived at Port Phillip, Australia on the 500-ton teak-built ship "Bengal Merchant" on September 2, 1852, 5 years after the last reference to him in the Glasgow newspapers in June 1847. The ship left London on April 1, and called in at Port Elizabeth, South Africa, on July 26 [32]. The "Bengal Merchant" appeared in an advertising poster of 1839, intimating its imminent departure from the Broomielaw Pier, Glasgow, taking passengers and cargo to New Zealand and The Colonies.

Lewellin's name appeared in the *Medical Register for the Colony of Victoria* from 1854 until 1886, and he was listed in a Melbourne *Directory* for 1858, as a dentist practising at 94 Collins Street, Melbourne [33]. A casual comment in one of his publications, in 1856 [34], stated ".. as I have now given up general practice and confine myself to Dentistry". It is not known if he was in general practice when he first arrived in Australia, or before he emigrated.

In 1861, he was listed as a surgeon, practising at 116 Chapel Street, Prahran [35]. Lewellin may by this time have been a general practitioner, perhaps conducting a mixed practice, including dentistry.

Lewellin's publications in Australia

Although Lewellin's name appeared only sporadically in the Australasian medical journals from 1856 onwards, the following three articles are of interest:

In 1856, Lewellin's address to the Medical Society of Victoria on "Acute Dysentery" was published in full [34].

In 1860, Lewellin presented a long and complex Case Report of "Pneumo-Hydro-Thorax" to the same Medical Society [36].

In 1863, Lewellin published a remarkable Case Report of a 12-year-old boy with tetanus [37], a condition for which the outlook in those days was hopeless. The boy developed hourly paroxysms of his back muscles, and Lewellin considered it advisable to remove a decayed tooth, which was acting as a source of irritation. He administered chloroform, and when the boy "was thoroughly under its influence, the rigidity abated sufficiently to allow me to get his mouth wedged open with a piece of soft wood, so that I extracted the first upper permanent molar of the left side, which was very much decayed. The second temporary molar of the lower jaw being also decayed, I removed that". The boy was so much improved as a result of the chloroform administration, that it was repeated at regular intervals every day for the next 12 days. During one of these administrations, Lewellin removed another decayed tooth. Chloroform undoubtedly resolved the spasms and delayed the onset of further spasms. On the 13th day, Lewellin recorded that paroxysms were becoming less frequent, although "he cannot do without chloroform". Ten days later, the boy "has become so fond of it that he flew into a passion when it was refused him". The boy appears to have recovered completely (no mention of hepatic necrosis!). This Case Report is notable for the diligent manner in which Lewellin attended his patient, and the determination with which he persisted with his treatment. This unique use of chloroform in the treatment of tetanus would only have been used by someone well versed in the problems of anaesthesia. There is no evidence that Lewellin had maintained his anaesthetic skills; indeed, the article gives the impression that he was now a General Practitioner.

Lewellin's friendship with Ferdinand von Mueller

Lewellin and his family became personal friends of the distinguished Botanist, Ferdinand von Mueller, who was born in Rostock, Germany and had, like Lewellin, emigrated to Australia. Mueller dedicated Volume 8 of his best known work, *Fragmenta Phytographiae Australiae* [38], to Lewellin, with a Latin inscription, which, translated, means "To my friend Henry Lewellin, a most skilful Physician".

Mueller named two plants after Lewellin: a shrub, named *Dicrastylis Lewellinii* [39], also called Purple Sand Sage [40], and a fungus, *Hygrophorus Lewellinae* [41]. In Volume 11 of *Fragmenta*, there is another reference to Lewellin [42], again in Latin, which translates ".. dedicated in gratitude to the distinguished Dr Henry Lewellin, the most generous promoter of my investigations"; Lewellin must have been sponsoring his friend's botanical studies.

Lewellin's death

Lewellin died on October 12, 1886, at his residence, Linton, Westbury Street, East St Kilda, Melbourne, in his 69th year [43, 44]. The Death Certificate, which recorded him as "Surgeon", indicates that he died three days after a hemiplegia, complicated by epileptic convulsions. It records his marriage in London, aged 26 years, to Grace Elizabeth Donnelly. She died in St Kilda, on August 7, 1888, aged 63 years [45]. She would have been 19 when she married Lewellin in 1844. It establishes that Lewellin was already married when he came to Glasgow in 1845. They had seven children.

Why did Lewellin move from Paris to Glasgow?

If Lewellin came directly from Paris to Glasgow in December 1845, he was leaving a city which was experiencing widespread social unrest. The working classes were being driven to the utmost limits of their resources. Lewellin may have sensed that civil war was imminent. Glasgow in 1845 would have provided a stimulating environment for any professional young man.

Why did he leave Glasgow in July 1847?

One can imagine many reasons why Lewellin left Glasgow. Perhaps his practice had not flourished. Perhaps he had upset his dental colleagues. Perhaps he was suffering once again from the wanderlust which seems to have been his hallmark during these early years. Perhaps it was the smoke and the climate that chased him away. Glasgow in 1847 was experiencing severe civil discontent, precipitated by deteriorating living conditions in many parts of the city, made worse by the large influx of Irish immigrants, after the potato famine of 1845. The poor were starving. There was no social support. Law and Order was beginning to break down, and the Bread Riots brought serious disruption to the city.

It is not yet known where he and his wife went for the next 5 years, but, with his entrepreneurial personality, it would almost certainly have been somewhere professionally stimulating. Australia and Melbourne would have fitted that category very well, but it was to be a further 5 years before he and his family landed at Port Phillip Bay.

Epilogue

The story of John Lewellin's life and career is incomplete. It is not known when he left Calcutta with his mother and brother, or where he lived until 1842, when he studied at St Bartholomew's. It is also not known when or for how long he was in Paris, Heidelberg, or the other European centres at which he studied. The most disappointing and frustrating gap is the 5-year period from June 1847 when he left Glasgow until September 1852 when he arrived in Australia.

The life of Lewellin provides an interesting, and at times exciting, tale of an enterprising pioneer. He showed initiative, by travelling around Europe to gain the widest experience by training in the most advanced centres. He showed charisma, by his conspicuous and flamboyant advertising of his dental skills during his time in Glasgow. He demonstrated courage, by being the first in Glasgow to administer ether in dental practice, integrity, by bringing his own experiences so promptly to the notice of the public, and remarkable clinical insight, by the perceptive observations which he recorded in such detail. He continued to display this dedicated approach to his work as a general practitioner in Australia, where he maintained his active role in medical affairs.

John Henry Hill Lewellin deserves credit and commendation for all these attributes. He has the distinction of being the first to have administered ether to a patient in Glasgow. If William Scott's anaesthetic to his patient in the Dumfries and Galloway Royal Infirmary on Saturday December 19, 1846 did indeed go badly wrong, then perhaps John Lewellin administered the first successful anaesthetic in Scotland on Monday January 4, 1847.

ACKNOWLEDGEMENTS

I have great pleasure acknowledging the help I received from three Australian colleagues: Professor John Pearn, University of Brisbane, Dr Gwen Wilson, Royal Australasian College of Surgeons, and Dr Richard Gillespie, University of Melbourne. I am most indebted to them for their interest and encouragement.

I am also grateful to Dr Derek Dow, Archivist to the Greater Glasgow Health Board; Dr Richard Ellis, St Batholomew's Hospital; Miss Elspeth King, Deputy Keeper of Local History, Glasgow Museums and Art Galleries; Mr Ian Lyle, Librarian at The Royal College of Surgeons of England; Dr Henry Noble, Glasgow Dental Hospital and School; Miss Judy Macdonald, State Library of Victoria, Australia: Dr Tom Boulton, Honorary Archivist to the Association of Anaesthetists of Great Britain and Ireland; and Dr Anima Banerjee, Calcutta, for providing the booklet, *The Fort*.

I wish to thank sincerely my colleagues in the Victoria Infirmary who assisted in the secretarial, research and photographic needs of this paper: Mrs Sheila Grant, Anaesthetic Department Secretary; Miss Sheila Murdoch, previously Librarian; and Mr Ian Taylor and his colleagues in the Medical Illustration Department. I am grateful also to Mrs Clare McMillan, Dorking, and Mrs Betty Thomson, Richmond, for research assistance; to Miss Anne Welsh and Mr Sidney Clarke, Royal Botanic Garden, Edinburgh; to Mr Geoffrey Yeo, Archivist at St Bartholomew's Hospital; and to the staff of the Photographic Department at the People's Palace, Glasgow.

REFERENCES

1. Sykes WS. *Essays on the First Hundred Years of Anaesthesia*, Vol. 1. Edinburgh: Churchill Livingstone, 1960; 48–76.
2. Baillie TW. *From Boston to Dumfries*. Dumfries: Dinwoodie and Co., 1966.
3. *Edinburgh Evening Courand* 1847; January 14.
4. *Glasgow Courier* 1847; January 16.
5. *Glasgow Herald* 1847; January 29.
6. Richardson BW. *Vita Medica: Chapters of Medical Life and Work*. London: Longman and Co., 1897; 57–99.
7. *Glasgow Herald* 1847; February 12.
8. *Glasgow Courier* 1847; January 1.
9. *Glasgow Courier* 1847; January 5.
10. *Glasgow Argus* 1847; January 11.
11. *Glasgow Herald* 1847; January 15.
12. *Glasgow Courier* 1847; January 16.
13. *Glasgow Courier* 1847; January 28.
14. *Glasgow Courier* 1847; January 26.
15. Buchanan G. Anaesthesia Jubilee: a retrospect. *Edinburgh Medical Journal* 1897; 1: 1–5.
16. *Glasgow Argus* 1847; January 21.
17. Boott F. Surgical operations performed during insensibility, produced by the inhalation of sulphuric ether. *Lancet* 1847; 1: 5–8.
18. *Glasgow Argus* 1847; February 1.
19. *Glasgow Argus* 1847; April 11.
20. *Glasgow Argus* 1847; June 21.
21. *Glasgow Argus* 1847; February 18.
22. *Glasgow Herald* 1845; December 15.
23. Bennet JH. *An Address Delivered to the Members of the Parisian Medical Society*. Paris: Moquet and Co., 1841.
24. Brown A. *History of Glasgow, Book 2, "Select Views"*. Glasgow: Joseph Swan, 1829; 190.
25. *Australian Medical Journal* 1868; 224.
26. *Australian Medical Journal* 1864; 30.
27. *Australian Medical Journal* 1867; 127.
28. *Medical Directory* 1878; 1150.
29. Singh, Brigadier G. *Our Fort*: 1953 (Publisher not recorded).
30. *Schedule of Deaths*. District of St Kilda, Melbourne, 1886.
31. *Marriages at the Out Stations 1808*. Bengal Presidency, India Office Library, N/1/8 Folio 91.
32. Biddle TE. *Transactions of British Ships Between Ports in the United Kingdom and the Port of Melbourne 1840–59*. Melbourne: State Library of Victoria.
33. *Sands and Kelly Directory*. Melbourne, 1858.

34. Lewellin JHH. Acute dysentry. *Australian Medical Journal* 1856; 196–202.
35. *Sands and Kelly Directory*. Melbourne, 1861.
36. Lewellin JHH. Pneumo-hydro-thorax. *Australian Medical Journal* 1860; 43–50.
37. Lewellin JHH. On a case of idiopathic tetanus, treated by aconite and chloroform. *Australian Medical Journal* 1863; 88–92.
38. Mueller F. von. *Fragmenta Phytographiae Australiae*, 1878–1881; 8.
39. Cunningham GM, Mulham WE, Milthorpe PL, Leigh JH. *Plants of New South Wales*. New South Wales: New South Wales Government Printing Office, in association with the Soil Conservation Service of New South Wales, 1981.
40. Munir AA. Taxonomic revision of Chloanthaceae trib. Physopsideae. *Brunonia* 1978; 1: 508–513.
41. Fuhrer B. *A Field Companion to Australian Fungi*. Hawthorn: The Five Mile Press, 1985.
42. Mueller F. von. *Fragmenta Phytographiae Australiae* 1878–1881; **11**: 86.
43. *Australasian Medical Gazette* 1886; 55.
44. *Australian Medical Journal* 1886; 484.
45. *Australian Medical Journal* 1888; 392.

British Journal of Anaesthesia 1993; **70**: 235–239

CORRESPONDENCE

NEUROMUSCULAR BLOCKERS IN DAY-CASE SURGERY: IS SPEED OF ONSET MORE IMPORTANT THAN DURATION OF ACTION?

Sir,—We read with interest the article by Cooper and colleagues [1] and would like to congratulate the authors. However, we believe that another perspective needs to be addressed. Cooper and colleagues and Pühringer and colleagues [2], compared intubating conditions in adults using either suxamethonium or Org 9426 (rocuronium), examining "rapid onset" and "good/excellent" intubating conditions. However, they did not focus on "rapidity of offset" of neuromuscular block, and we feel much more attention should be directed to this aspect.

In a study by Lippmann and colleagues [3], using vecuronium in a dose of 0.05 mg kg^{-1} (corresponding to the ED$_{95}$), a mean onset time of 148 s (range 90–240 s) was recorded. Although this onset time is slightly longer than that of rocuronium, it was noted that the offset time for vecuronium was only 22 min compared with the offset time for rocuronium of 30–36 min noted in other studies [1, 2]. We feel it is important to recognize that Lippmann and colleagues also achieved excellent/good intubating conditions in 95% of patients studied. Mirakhur and colleagues [4] used much smaller doses (0.1–0.2 mg kg^{-1}) than in the present study and, under these conditions, noted "satisfactory" intubating conditions in only 90% of patients, taking 90 s to achieve those conditions. Moreover, duration of action of up to 71 min was recorded, much different from that noted in the paper by Cooper and colleagues. While anaesthetic techniques differed (use of volatile agent *vs* opioids), these data would suggest that the advantage of rocuronium ultimately may be a rapid onset; however, a longer duration of action may outweigh this benefit, especially when used at the greater ED$_{95}$ dose range.

As outpatient surgery does not require rapid intubation, rapid offset of neuromuscular block is more often required. Perhaps future studies should be directed to comparing (low-dose) rocuronium with low-dose vecuronium, rather than with suxamethonium.

M. Lippmann
R. Ginsburg
Harbor – UCLA Medical Center
Torrance, California

1. Cooper R, Mirakhur RK, Clarke RSJ, Boules Z. Comparison of intubating conditions after administration of Org 9426 (rocuronium) and suxamethonium. *British Journal of Anaesthesia* 1992; **69**: 269–272.
2. Pühringer F, Khuenl-Brady K, Koller J, Mitterschiffthaler C. Evaluation of the endotracheal intubating conditions of rocuronium (Org 9426) and succinylcholine in outpatient surgery. *Anesthesia and Analgesia* 1992; **75**: 37–40.
3. Lippmann M, Berman M, Gonzalez H, Appel P, Mok MS. Vecuronium for outpatient surgery in a teaching hospital. *Anesthesia and Analgesia* 1988; **67**: S134.
4. Mirakhur RK, Ferres CJ, Clarke RSJ, Bali IM, Dundee JW. Clinical evaluation of Org NC45. *British Journal of Anaesthesia* 1983; **55**: 119–124.

Sir,—Thank you for the opportunity to reply to the letter by Drs Lippmann and Ginsburg. We agree that the duration of action of vecuronium 0.05 mg kg^{-1} is shorter than that of rocuronium 0.6 mg kg^{-1}. This is not surprising because, in terms of potency, this dose of rocuronium is about twice that of vecuronium. Most other claims made by Drs Lippmann and Ginsburg, however, are not supported by the evidence they have quoted [1]. They contend that a mean onset time of 148 s for vecuronium 0.05 mg kg^{-1} is only slightly longer than that of rocuronium 0.6 mg kg^{-1}, which was about 89 s. However, not only is 148 s much longer than 89 s, but Lippmann and Ginsburg fail to point out that this time of 148 s was the time only to the start of effect of vecuronium (compared with 25.8 s for rocuronium in our study), and that the time to complete block in their study varied from 6.5 to more than 7 min, even when isoflurane was used. This time for rocuronium was 89 s. In addition, monitoring of neuromuscular block in their study did not appear to use any means of accurately measuring the block.

Excellent to good intubating conditions in 95% of patients after vecuronium 0.05 mg kg^{-1}, which they quote in their letter (assessed at what time?), appear to be a personal impression, because there are no data on intubating conditions given in the paper they have quoted [1]. They state clearly the advantage of using an agent such as vecuronium in outpatient surgery, yet fail to appreciate that, at equipotent doses, there is little difference between rocuronium and vecuronium in duration of action. Rocuronium, in addition, has the advantage of a rapid onset of action and provision of documented good intubating conditions within 60–90 s [2–4].

It appears that the effect of vecuronium had to be antagonized even after only 0.05 mg kg^{-1} was used in the study by Lippmann and colleagues [1], in which surgery lasted about 47 min. A single dose of rocuronium 0.5–0.6 mg kg^{-1} as used in recent studies would provide better relaxation for procedures of this duration and could be antagonized easily in the same way.

R. K. Mirakhur
R. A. Cooper
R. S. J. Clarke
Z. Boules
Queens University
Belfast

1. Lippmann M, Mok MS, Berman M, Gonzalez H. Vecuronium for outpatient surgery. *Anesthesia and Analgesia* 1988; **67**: S134.
2. Cooper RA, Mirakhur RK, Clarke RSJ, Boules Z. Comparison of intubating conditions after administration of Org 9426 (rocuronium) and suxamethonium. *British Journal of Anaesthesia* 1992; **69**: 269–272.
3. Pühringer S, Khuenl-Brady K, Koller J, Mitterschiffthaler C. Correlation of the endotracheal intubating conditions of rocuronium (Org 9426) and succinylcholine in outpatient surgery. *Anesthesia and Analgesia* 1991; **75**: 37–40.
4. Huizinga ACT, van den Brom RHG, Wierda JMKH, Hommes SPM, Hennis PJ. Intubating conditions and onset of neuromuscular block of rocuronium (Org 9426): a comparison with suxamethonium. *Acta Anaesthesiologica Scandinavica* 1992; **36**: 463–468.

BLOOD LOSS DURING TOTAL HIP REPLACEMENT

Sir,—We wish to comment on the letter by Drs McSwiney, Joshi and McCaroll [1].

We reviewed 47 patients in the early 1980s who had received cemented Stanmore hip prostheses. They were anaesthetized with thiopentone, nitrous oxide, oxygen and halothane, supplemented with extradural analgesia. Systolic arterial pressure was maintained at 100 mm Hg with infusions and volatile agents.

We found that 21% (10 patients) required no blood and 47% (23 patients) did not require blood in theatre, estimated by swab weighing and suction drainage measurement.

Of the group that required no blood, the maximum decrease in haemoglobin was 2.2 g dl^{-1}, measured on the third day after operation except for one patient whose Hb decreased by 4.2 g dl^{-1} from a value of 16.0 g dl^{-1}. The decrease in haemoglobin concentration may be physiologically advantageous considering the decrease in blood viscosity.

We wish to draw attention to our reliance on the extradural technique for achieving these conditions.

N. O. Jones
J. G. Guy
Worcester Royal Infirmary
Worcester

1. McSwiney M, Joshi G, McCaroll M. Blood loss during total hip replacement. *British Journal of Anaesthesia* 1992; **69**: 331–332.

Sir,—We thank you for the opportunity to comment on the letter by Drs Jones and Guy. They state that 21% of their patients required no blood transfusion, compared with 68% of our study group. Forty-seven percent of their patients did not require transfusion during surgery, whereas no patient in our study group required such transfusion. All the patients in their study had their surgery performed under a combination of general anaesthesia supplemented with extradural analgesia; 92.5% of our group had spinal anaesthetics with only 7.5% having general anaesthesia.

The emphasis of our study was the impact of transfusion trigger guidelines on transfusion requirements for total hip replacement surgery. It would be interesting to known what criteria Drs Jones and Guy used to define the need for transfusion, as they do not appear to have reduced their transfusion requirement to the same extent.

In addition, there were no statistically significant differences in postoperative complications between our control and study groups, although the control group had a greater proportion of wound infections and thrombotic events.

M. McSwiney
Bristol Royal Infirmary
Bristol

METABOLIC EFFECTS OF DOBUTAMINE

Sir,—Dr Bhatt and colleagues [1] should be congratulated on their attempts at defining the relationship between oxygen consumption ($\dot{V}O_2$) and oxygen delivery ($\dot{D}O_2$) in relation to the thermogenic effect of dobutamine. We agree with the view they express that the thermogenic effects of inotropes, and thus the increased demand for oxygen and the ensuing "need" for an increase in cardiac output, has been understated in previous discussions of the $\dot{V}O_2/\dot{D}O_2$ relationship in critical illness. Their results bear out those of Ruttiman and colleagues [2] with dopamine, and our own work on the metabolic effects of both dopamine and dobutamine [3, 4]. We demonstrated an increase in energy expenditure of 33% with dobutamine at 10 μg min^{-1} kg^{-1}, compared with an increase of 24% in $\dot{V}O_2$ that they described at an infusion rate of 7.5 μg min^{-1} kg^{-1}. We found also a massive increase in circulating free fatty acid (FFA) and glycerol concentrations, and ascribed the increase in energy expenditure to increased FFA–triglyceride cycling.

Two features of the results that they presented but did not discuss further were the decrease in both noradrenaline and blood glucose concentrations. We described similar findings; the decrease in endogenous catecholamines was ascribed to the inhibitory effect of a very large increase in arterial pressure on sympathetic nervous activity, and that in blood sugar to an increase in insulin secretion, which we also demonstrated. This in turn was presumed to be attributable to the marked beta effects of the infused dobutamine.

The assertion that the increase in $\dot{V}O_2$ seen in association with an increase in cardiac output in critical illness is a result of an increase in peripheral perfusion (while the thermogenic effect of the inotropic drug used is ignored) has gone unchallenged for too long. Dr Bhatt is to be commended on bringing it to our attention.

I. T. Campbell
Withington Hospital
Manchester
C. J. Green
Zoetemeer
Netherlands

1. Bhatt SB, Hutchinson RC, Tomlinson B, Oh TE, Mak M. Effect of dobutamine on oxygen supply and uptake in healthy volunteers. *British Journal of Anaesthesia* 1992; **69**: 298–303.
2. Ruttiman Y, Chiolero R, Jequier E, Brietenstein E, Schutz Y. Effects of dopamine on total oxygen consumption and oxygen delivery in healthy man. *American Journal of Physiology* 1989; **257**: E541–E546.
3. Regan CJ, Duckworth R, Fairhurst JA, Maycock PF, Frayn KN, Campbell IT. Metabolic effects of low dose dopamine infusion in normal volunteers. *Clinical Science* 1990; **79**: 605–611.
4. Green CJ, Frazer RS, Underhill S, Maycock P, Fairhurst JA, Campbell IT. Metabolic effects of dobutamine in normal man. *Clinical Science* 1992; **82**: 77–83.

Sir,—The paper by Bhatt and colleagues [1] examined the relationship between oxygen delivery ($\dot{D}O_2$) and oxygen consumption ($\dot{V}O_2$) in healthy volunteers, on the premise that there is no tissue oxygen debt at rest in health. However, they stated that the serum lactate concentration decreased after infusion of dobutamine, and returned to the baseline value when the dobutamine was stopped. Systemic vascular resistance index (SVRI—calculated from table I) also decreased during dobutamine infusion, although mean arterial pressure increased; could this not imply an improvement in tissue perfusion with a consequent reduction in serum lactate during dobutamine infusion in healthy volunteers? As $\dot{D}O_2$ increased during the study at each infusion rate of dobutamine, the conclusion that the increase in $\dot{V}O_2$ was caused by the calorigenic effect of dobutamine cannot be inferred with certainty from the results presented. Bizouarn and colleagues [2] have shown a significant and variable difference between $\dot{V}O_2$ measurements by indirect calorimetry compared with those calculated by the Fick principle, except during cardiopulmonary bypass (CPB). Bhatt and colleagues computed $\dot{D}O_2$ from a combination of thoracic impedance plethysmography and pulse oximetry, neither of which are "gold standards", and then correlated this with $\dot{V}O_2$ measured by indirect calorimetry. The greater increase in $\dot{D}O_2$ compared with $\dot{V}O_2$ may therefore reflect differences between methods rather than a true discrepancy.

In a preliminary study (unpublished) of three patients during stable CPB at 25 °C, we have examined the effect of dobutamine infusion on VO_2 while holding DO_2 constant. Compared with a baseline before dobutamine infusion, $\dot{V}O_2$ increased by 14.8%, 17.9% and 15.7% in the three patients after 15 min of dobutamine 7.5 μg kg^{-1} min^{-1}. In two patients, $\dot{V}O_2$ had returned to the baseline value 15 min after the dobutamine was stopped (rewarming had started before the end of the 15 min in the other patient). Bhatt and colleagues may have been correct in their *assumption* that the discrepancy between $\dot{D}O_2$ and $\dot{V}O_2$ in their study indicated a calorigenic effect of dobutamine, but our results provide direct evidence for an increase in metabolic rate during dobutamine infusion.

We were puzzled by the data handling and statistics in their paper. First, the $\dot{D}O_2$ and $\dot{V}O_2$ data are presented as line graphs, implying a continuous relationship between measurement points, rather than as bar charts. As $\dot{V}O_2$ and $\dot{D}O_2$ were measured every 5 min, we wonder why the intermediate data points were not presented in the paper; it would be interesting to know how quickly the $\dot{D}O_2$ and $\dot{V}O_2$ measurements reached a plateau after each change of infusion rate. Second, in table I a decrease in serum lactate from 1.3 (SEM 0.1) to 1.2 (0.1) mmol litre^{-1} is statistically insignificant, while an increase from 1.2 (0.1) to 1.3 (0.1) mmol litre^{-1} is significant; this does not appear consistent.

The interpretation in the discussion of changes in plasma noradrenaline concentration is confusing. The results of Bhatt and colleagues in healthy volunteers (mean noradrenaline concentration 140 ng litre^{-1}) were compared with a group of patients in chronic heart failure (CHF) in whom the mean noradrenaline concentration was 518 ng litre^{-1} [3]. The CHF patients presumably suffered from down-regulation of their beta receptors. Bhatt and colleagues then quoted Sjöström and colleagues [4] to state that a decrease of 160 ng litre^{-1} in the noradrenaline concentration in the CHF patients was "metabolically insignificant", but Sjöström's group studied the effect of adrenaline infusion in healthy women and measured the plasma noradrenaline response. In any event, in Sjöström's study, infusion of adrenaline 0.01 μg kg^{-1} min^{-1} produced a 300% increase in plasma adrenaline, associated with a 14% increase in plasma noradrenaline (from 169 to 193 ng litre^{-1}) and an 8.3% increase in resting metabolic rate. Sjöström did not determine if the adrenaline or the noradrenaline was responsible for the significant increase in metabolic rate.

D. C. Smith
C. M. Dryden
M. A. Hume
Western Infirmary
Glasgow

1. Bhatt SB, Hutchinson RC, Tomlinson B, Oh TE, Mak M. Effect of dobutamine on oxygen supply and uptake in healthy volunteers. *British Journal of Anaesthesia* 1992; **69**: 298–303.
2. Bizouarn P, Soulard D, Blanloeil Y, Guillet A, Goarin Y. Oxygen consumption after cardiac surgery—a comparison between calculation by Fick's principle and measurement by indirect calorimetry. *Intensive Care Medicine* 1992; **18**: 206–209.
3. Colucci WS, Denniss AR, Leatherman GF, Quigg RJ, Ludmer PL, Marsh JD, Gauthier DF. Intracoronary infusion of dobutamine to patients with and without severe congestive heart failure. *Journal of Clinical Investigation* 1988; **81**: 1103–1110.
4. Sjöström L, Shutz Y, Gudinchet F, Hegnell L, Pittet PG, Jéquier E. Epinephrine sensitivity with respect to metabolic rate and other variables in women. *American Journal of Physiology* 1983; **245**: E431–E442.

Sir,—We thank Drs Campbell and Green for their comments on our report. Their detailed study on the metabolic effects of dobutamine [1] had not been published at the time that our article [2] was submitted, so we were pleased to see that their results and conclusions were in close agreement with our own.

In addition to demonstrating the calorigenic effect of dobutamine, both studies showed decreases in plasma concentrations of noradrenaline and glucose. We did not speculate on the cause of the decrease in noradrenaline concentration, but would agree with their suggestion that it is caused by a reduction of sympathetic activity secondary to the increase in arterial pressure. This explanation is supported by the observation that the muscle sympathetic activity as measured by microneurography is reduced during dobutamine infusion [3].

The decrease in blood glucose concentration during dobutamine infusion would, at least in part, be explained by their finding of increased concentrations of insulin. This appears to be brought about by a beta$_2$ adrenoceptor stimulation [4]. Adrenaline causes a reduction in plasma concentrations of insulin at least during the early phase of an infusion which is probably a result of alpha$_2$ adrenoceptor stimulation [5]. As the alpha agonist activity of dobutamine is predominantly alpha$_1$ [6], the beta$_2$ adrenoceptor agonist effect becomes apparent here.

We share the view of Drs Campbell and Green that the inherent metabolic effects of catecholamines should be considered when demonstrating supply dependence of oxygen uptake or identifying "covert" tissue hypoxia.

We appreciate also the interest shown by Drs Smith, Dryden and Hume, and are sorry that they are confused by their interpretation of our paper [2]. We shall explain the many and varied points raised by them.

First, they implied that our plasma lactate concentrations were perfusion-dependent, which would presuppose that our subjects had some perfusion-limited tissue hypoxia. However, the plasma lactate concentrations of our subjects, who were young, healthy and at rest, remained within normal limits before, during and after the infusions of dobutamine. Plasma lactate concentration results from a balance between continual production and metabolism [7] and, furthermore, normal values in healthy subjects at rest do not imply perfusion-limited tissue hypoxia [8].

We are pleased that Drs Smith, Dryden and Hume are aware that $\dot{V}\mathrm{o}_2$ values calculated by the Fick principle (c$\dot{V}\mathrm{o}_2$) and those measured by indirect calorimetry (m$\dot{V}\mathrm{o}_2$) are different. They quoted the work by Bizouarn and colleagues who, with others, have recently shown that c$\dot{V}\mathrm{o}_2$ and m$\dot{V}\mathrm{o}_2$ values are not interchangeable [9–11]. Bizouarn and colleagues also listed possible causes of errors for both methods, but did not suggest or imply that measured $\dot{V}\mathrm{o}_2$ is less accurate than calculated $\dot{V}\mathrm{o}_2$. Indeed, those authors acknowledged that "the precision of the measurements (of m$\dot{V}\mathrm{o}_2$ using the Deltatrac monitor) remains satisfactory". In fact, the major criticism of studies reporting pathological dependence of $\dot{V}\mathrm{o}_2$ on $\dot{D}\mathrm{o}_2$ is the use of c$\dot{V}\mathrm{o}_2$ with its inherent flaw in mathematical coupling [12]. Measured $\dot{V}\mathrm{o}_2$ was the correct method to use in our study. The accuracy of the Deltatrac monitor has been validated [13, 14], and all the potential sources of error associated with its use [9] were absent in our study. We used a non-invasive method to measure cardiac output because we rejected the use of the thermodilution technique in awake, healthy subjects (and most, if not all, Ethics Committees would also agree). The thoracic impedance technique is not a "gold standard", but variations of 10–20% in the thermodilution measurement of cardiac output are also recognized. It was also acceptable for us to record oxygen saturation in unanaesthetized, young, healthy subjects at rest using a pulse oximeter (Sp_{O_2}). The variation in Sp_{O_2} and the oxygen saturation measured by a co-oximeter in these subjects at rest is negligible, and this has been confirmed by one of us (using the method of Bland and Altman [15]) in preparatory work for a previous study [16].

We did not assume "that the discrepancy between $\dot{D}\mathrm{o}_2$ and $\dot{V}\mathrm{o}_2$ indicated a calorigenic effect of dobutamine" (whatever that implies), as claimed by Drs Smith, Dryden and Hume. We showed an increase in $\dot{V}\mathrm{o}_2$ during infusions of dobutamine in healthy subjects at rest.

As regards "data handling and statistics", bar charts may be less confusing to Drs Smith, Dryden and Hume, but the description of our method and results clearly did not suggest "a continuous relationship between measurement points". As for intermediate data points, we did not measure $\dot{V}\mathrm{o}_2$ and $\dot{D}\mathrm{o}_2$ "every 5 min" as they had mistakenly interpreted. We used the repeated measures analysis of variance and the significance of any difference may not be apparent from the mean values alone. Part of Drs Smith, Dryden and Hume's puzzlement would be alleviated if we express the results fully rather than rounding off at a single decimal place—that is, the plasma lactate concentrations at baseline, with 2.5-, 5.0- and 7.5-μg kg^{-1} min^{-1} infusions and after infusion were 1.436 (SEM 0.085), 1.248 (0.043), 1.204 (0.045), 1.23 (0.052) and 1.348 (0.068) mmol litre^{-1}, respectively.

Drs Smith, Dryden and Hume also misinterpreted our discussion on the metabolic effects of catecholamines. We did not compare changes in noradrenaline concentration in our subjects with those reported by Collucci [17]. We put into perspective the report of Vincent and colleagues [18] that $\dot{V}\mathrm{o}_2$ was not increased after dobutamine infusion in critically ill patients without lactic acidosis; those authors cited Collucci's paper in support of their hypothesis of an attenuated endogenous catecholamine response. Drs Smith, Dryden and Hume also claimed that we quoted Sjöström and colleagues [19] "to state that a decrease of 160 ng litre^{-1} in the noradrenaline concentration in CHF patients was 'metabolically insignificant'". They must have a different edition of the Journal, as we cannot find that statement either as quoted or implied, in our edition or manuscript. We simply suggested that noradrenaline is probably a less potent calorigenic agent than adrenaline [19, 5].

Finally, Drs Smith, Dryden and Hume drew attention to their series of three patients (unpublished) in whom metabolic rate increased during dobutamine infusion. Indeed, that was also our findings and that of Green and colleagues [1] who, unknown to us, were also studying the subject at the same time.

T. E. Oh
S. B. Bhatt
B. Tomlinson
Prince of Wales Hospital, Shatin
Hong Kong

1. Green CJ, Frazer RS, Underhill S, Maycock P, Fairhurst JA, Campbell IT. Metabolic effects of dobutamine in normal man. *Clinical Science* 1992; **82**: 77–83.
2. Bhatt SB, Hutchinson RC, Tomlinson B, Oh TE, Mak M. Effect of dobutamine on oxygen supply and uptake in healthy volunteers. *British Journal of Anaesthesia* 1992; **69**: 298–303.
3. Schobel HP, Ozen RM, Roach PJ, Mark AL, Ferguson DW. Contrasting effects of digitalis and dobutamine on baroreflex sympathetic control in normal humans. *Circulation* 1991; **84**: 1118–1129.
4. Arnold JMO, O'Connor PC, Riddel JG, Harron DWJ, Shanks RG, McDevitt DG. Effects of the β_2 adrenoceptor agonist ICI 118,551 on exercise tachycardia and isoprenaline induced β adrenoceptor responses in man. *British Journal of Clinical Pharmacology* 1985; **19**: 619–630.
5. Macdonald IA, Bennet T, Fellows IW. Catecholamines and the control of metabolism. *Clinical Science* 1985; **68**: 613–619.
6. Ruffolo RR jr, Yaden EL. Vascular effects of sterio isomers of dobutamine. *Journal of Pharmacology and Experimental Therapeutics* 1983; **224**: 46–53.
7. Kreisberg RA. Glucose–lactate inter-relations in man. *New England Journal of Medicine* 1972; **287**: 132–137.
8. Brooks GA. Lactate production under fully aerobic

conditions: the lactate shuttle during rest and under exercise. *Federation Proceedings* 1986; **45**: 2924–2929.

9. Bizouarn P, Soulard D, Blanloeil Y, Guillet A, Goarin Y. Oxygen consumption after cardiac surgery—a comparison between calculation by Fick's principle and measurement by indirect calorimetry. *Intensive Care Medicine* 1992; **18**: 206–209.
10. Vermeij CG, Feenstra BWA, Bruining HA. Oxygen delivery and oxygen uptake in postoperative and septic patients. *Chest* 1991; **98**: 415–420.
11. Ronco JJ, Phang PT, Walley KR, Wiggs B, Fenwick JC, Russell J. Oxygen consumption is independent of changes in oxygen delivery in severe adult respiratory distress syndrome. *American Review of Respiratory Disease* 1991; **143**: 1267–1273.
12. Crone D. Oxygen supply and oxygen consumption: Does pathological oxygen supply-dependency exist? In: Kerr D, Thirlwell J, eds. *Australasian Anaesthesia 1992*. Melbourne: ANZCA, 1992; 101–107.
13. Takala J, Keinanen O, Vaisanen P, Kari A. Measurement of gas exchange in intensive care: laboratory and clinical validation of a new device. *Critical Care Medicine* 1989; **17**: 1041–1047.
14. Makita K, Nunn JF, Royston B. Evaluation of metabolic measuring instruments for use in critically ill patients. *Critical Care Medicine* 1990; **18**: 638–644.
15. Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet* 1986; **1**: 307–310.
16. Oh TE, Ferguson MR. Suctioning hypoxaemia. *Anaesthesia and Intensive Care* 1989; **17**: 224.
17. Collucci WS, Denniss RA, Leatherman GF, Quigg RJ, Ludmer PL, Marsh JD, Gauthier DF. Intracoronary infusion of dobutamine to patients with and without heart failure: dose response relationships, correlation with circulating catecholamines and effect of phosphodiesterase inhibition. *Journal of Clinical Investigation* 1988; **81**: 1103–1110.
18. Vincent JL, Roman A, Backer DD, Kahn RJ. Oxygen uptake/supply dependency. Effects of short term dobutamine infusion. *American Review of Respiratory Disease* 1990; **142**: 2–7.
19. Sjöström L, Schutz Y, Gudinchet F, Hegnell L, Pittet PG, Jequier E. Epinephrine sensitivity with respect to metabolic rate and other variables in women. *American Journal of Physiology* 1983; **245**: E431–E442.

NITROUS OXIDE ADMINISTRATION VIA OXYGEN THERAPY DEVICES

Sir,—I was interested to read the paper by Joshi, Ooi and Soni [1] on nitrous oxide administration using oxygen therapy devices. Of particular interest to me were the widely divergent results obtained when comparing the Hudson and Vickers air entrainment masks, using a flow of 50% oxygen–50% nitrous oxide (e.g. 40% mask—nitrous oxide: Hudson 6.5%, Ventimask 13.6%). I was concerned also to see that, in calculating a theoretical concentration of nitrous oxide, these workers chose to assume that altering the composition of the primary flow does not affect the entrainment ratio.

I have previously studied the Accurox air entrainment masks using a primary flow of Entonox [2]. I think it is worth noting that the nominal 35% and 50% blenders from this manufacturer provided concentrations of oxygen and nitrous oxide similar to those reported by Joshi for the Hudson 40% and Ventimask 40%, respectively.

The function of air entrainment oxygen masks is best explained by the process of constant-pressure jet mixing [3]. The equations governing B, the mass entrainment ratio (entrained mass flow: jet mass flow), are complex. However, for a given volume flow, a jet of 50% oxygen–50% nitrous oxide has a mass that is 18.75% greater than that of a jet of oxygen. Thus, even if B is unaffected by the change in primary flow, an increase in volume of entrained air of 18.75% would be predicted. My own data demonstrated an increase in entrained flow of 13% (range 5–27%) in Accurox masks. I do not accept the assumption, therefore, that altering the composition of the primary flow does not affect the entrainment ratio.

Identical masks from the same manufacturer, using either oxygen or Entonox, reliably produce the same concentrations of gases, and masks from many manufacturers, using a primary flow of 100% oxygen, provide oxygen enriched air at near specified concentrations. However, substitution of the primary flow by Entonox appears to provide quite varied concentrations of nitrous oxide and oxygen from the masks of differing manufacturers with similar nominal specifications.

I feel that the available data demonstrate an important point that is not emphasized by Joshi and colleagues. Air entrainment masks of different manufacturers cannot be relied upon to produce similar final concentrations when the primary flow is not 100% oxygen. Application of simple theoretical calculations are inappropriate and unreliable in attempting to predict the performance of these masks with a primary flow of Entonox, and the use of these masks with a primary flow other than 100% oxygen should be strongly discouraged.

J. M. Goddard
Children's Hospital
Sheffield

1. Joshi P, Ooi R, Soni N. Nitrous oxide administration using commonly available oxygen therapy devices. *British Journal of Anaesthesia* 1992; **68**: 630–632.
2. Goddard JM. Postoperative nitrous oxide analgesia. Administration from air entrainment oxygen masks with a primary flow of Entonox. *Anaesthesia* 1986; **41**: 915–918.
3. Scacci R. Air entrainment masks: jet mixing is how they work; The Bernoulli and Venturi principles are how they don't. *Respiratory Care* 1979; **24**: 928–931.

Sir,—Thank you for the opportunity to reply to Dr Goddard's letter. It is unfortunate that Dr Goddard has not read our article in detail. Our study was not a theoretical analysis of the performance characteristics of simple and fixed-performance masks. The values for the likely inspired concentrations of nitrous oxide and oxygen were not derived from mathematical predictions, but were actually measured from the "trachea" of a lung model.

We agree that an assessment of the nitrous oxide–oxygen delivery characteristics of such masks requires more complex models as used by Dorrington [1] in his analysis of gas transfer in oxygen delivery systems. However, for the purpose of only checking on the general validity of our experimental results, we avoided this mathematical maze and felt that a simplified formula was adequate. Indeed, the observed variation among the various fixed-performance masks, when looking at the differences between predicted and measured concentrations of the gases in the study, strongly suggest that there were no systematic differences arising from the simplified mathematical treatment applied.

P. Joshi
R. Ooi
Westminster Hospital
London

1. Dorrington KL. *Anaesthetic and Extracorporeal Gas Transfer*. Oxford: Clarendon Press, 1989.

MORTALITY IN ITU PATIENTS RECEIVING NEUROMUSCULAR BLOCKING DRUGS

Sir,—Some comment has been made on the fact that no mortality figures were quoted in one of our recent papers on the use of constant infusions of atracurium in critically ill patients in an intensive care unit [1].

In this series of 15 patients, seven of whom suffered combined renal and respiratory failure and eight of whom had respiratory failure but normal renal function, the ITU mortality in the former group was 43%, and in the latter group, 25%. These mortality figures are comparable to those reported in previously published studies [2–4].

We hope that those who have made much of this omission will, in future, quote these figures directly. However, it is our belief that comparison of data on mortality, gained retrospectively, is futile because of the disparity between patients. Some form of disease classification is necessary if it is to be effective [5]. However, we would support consideration of a controlled, prospective study of mortality in the critically ill who are receiving infusions of neuromuscular blocking drugs.

J. M. Hunter
E. S. Shearer
University of Liverpool
Liverpool

1. Shearer ES, O'Sullivan EP, Hunter JM. Clearance of atracurium and laudanosine in the urine and by continuous venovenous haemofiltration. *British Journal of Anaesthesia* 1991; **67**: 569–573.
2. Griffiths RB, Hunter JM, Jones RS. Atracurium infusions in patients with renal failure on an ITU. *Anaesthesia* 1986; **41**: 375–381.
3. Smith CL, Hunter JM, Jones RS. Vecuronium infusions in patients with renal failure on an ITU. *Anaesthesia* 1987; **42**: 387–393.
4. Yate PM, Flynn PJ, Arnold RW, Weatherly BC, Simmonds RJ, Dopson T. Clinical experience and plasma laudanosine concentrations during the infusion of atracurium in the intensive therapy unit. *British Journal of Anaesthesia* 1987; **59**: 211–217.
5. Kraus WA, Draper EA, Wagner DP, Zimmerman JE. Apache II: a severity of disease classification system. *Critical Care Medicine* 1985; **13**: 818–829.

FACE MASKS AND SPINAL ANAESTHESIA

Sir,—The wearing of face masks while performing spinal anaesthesia remains a controversial issue. Although there is little clear evidence for the transmission of infection to the patient during this procedure, we are reminded occasionally of the potential for serious morbidity [1]. It is therefore mandatory to consider the most appropriate way in which we can "pay attention to detail" [2] and attempt to prevent adverse events.

Philips and colleagues [3] have presented evidence to support the contention that masks are effective in reducing bacterial infection, and consequently recommended their use. However, we believe their conclusions to be flawed in one respect. They compared contamination of agar plates when subjects were talking at the plates with and without the use of a face mask. In their study, they did not examine the effect of the subject remaining mainly silent for the 5 min of the study period. If the aim is to find ways of eliminating transmission of bacteria, we feel that this aspect should be examined. It may be that remaining silent for most of the period of insertion of a spinal may itself help prevent the dispersal of upper airway organisms. Remaining mainly silent during the procedure need not compromise the anaesthetist's contact with the patient, as a full explanation of the procedure should be given before the start.

In order to examine the effect of speech on the dispersal of bacteria, we chose to simulate Philips and colleagues' study with 10 anaesthetists as subjects. The subjects were studied under three different conditions: sitting silently, 30 cm from an agar plate; sitting talking, 30 cm away from an agar plate; sitting talking and wearing a face mask, 30 cm away from an agar plate. All agar plates were incubated at 37 °C for 24 h and colonies grown were examined and counted by a microbiologist blinded to the conditions.

Our results were as follows. In group one (sitting silent) one subjects of 10 grew a total of one colony (0.1 colony/subject). In group two (talking without a face mask) five subjects of 10 grew a total of 44 colonies (4.4 colony/subject). In group three (talking with a face mask) three subjects of 10 grew a total of three colonies (0.3 colony/subject).

The large difference in numbers of colonies grown when the subject remained silent and when talking illustrates the importance of speech in the dispersal of upper airway organisms. This difference was significant at the $P < 0.01$ level when a paired Student's t test was performed. Although three times as many colonies were grown when talking while wearing a face mask compared with remaining silent without a face mask, this difference was not significant.

We suggest, therefore, that the act of speaking may itself promote the dispersal of bacteria from the upper airway, and that failing to control for this effect renders some of the conclusions of Philips and colleagues open to question. Face masks may help prevent the spread of bacteria, but our results show that remaining silent may achieve this aim at least as effectively. If the prevention of transmission of infection from the anaesthetist to the patient is paramount, then we suggest that the anaesthetist remain silent while performing spinal anaesthesia, whether a face mask is worn or otherwise.

S. W. O'Kelly
D. Marsh
Queen Alexandra Hospital
Portsmouth

1. Lee JJ, Parry H. Bacterial meningitis following spinal anaesthesia for Caesarean section. *British Journal of Anaesthesia* 1991; **66**: 383–386.
2. Wildsmith JAW. Regional anaesthesia requires attention to detail. *British Journal of Anaesthesia* 1991; **67**: 224–225.
3. Philips BJ, Fergusson S, Armstrong P, Anderson FM, Wildsmith JAW. Surgical face masks are effective in reducing bacterial contamination caused by dispersal from the upper airway. *British Journal of Anaesthesia* 1992; **69**: 407–408.

Sir,—Thank you for the opportunity to reply to the letter from Drs O'Kelly and Marsh. Their data are interesting and valid within a specific context. However, I believe it is unrealistic to propose that an anaesthetist should remain completely silent during the course of providing a spinal or extradural block, and I would even suggest that it would be bad practice to do so. I am amazed at the contortions that some wish to go through to avoid the taking of a simple, straightforward precaution. What motives are involved I cannot understand.

J. A. W. Wildsmith
Royal Infirmary
Edinburgh

PAIN ON I.V. INJECTION OF METOCLOPRAMIDE

Sir,—I was interested to read the report of Ganta and Fee [1] in which they described the use of metoclopramide 5 mg in an attempt to obtund the pain produced by induction of anaesthesia by propofol. Their work suggests that the drug is as effective for this purpose as the more commonly used lignocaine.

I have been using metoclopramide as an antiemetic for more than 2 yr. I give every patient I anaesthetize an i.v. bolus of metoclopramide 10 mg on induction, provided that there is no contraindication to its use. I have noted that if the drug is injected into a small vein on the dorsum of the hand, before any other agent, and especially in unpremedicated patients, more than 40% complain of a severe burning pain in the vein.

I believe that this response is recognized by those that use the "high dose" ampoules (100 mg) of metoclopramide in chemotherapy treatment, but not by anaesthetists. Interestingly, this side effect is not recorded in the relevant Data Sheets for this product [2]. I continue to use metoclopramide, but now administer the drug when the patient is asleep.

D. J. Wilkinson
St Bartholomew's Hospital
London

1. Ganta R, Fee JP. Pain on injection of propofol: comparison of lignocaine with metoclopramide. *British Journal of Anaesthesia* 1992; **69**: 316–317.
2. ABPI. *Data Sheet Compendium*. London: Datapharm, 1992; 148–150.

British Journal of Anaesthesia 1993; **70**: 240–241

BOOK REVIEWS

Principles and Protocols in Intensive Care. Edited by S. M. Willatts and R. J. Winter. Published by Portland Press Ltd, Colchester. Pp. 415; indexed. Price £29.50.

This text is a 400-page, soft covered volume which is divided into 12 sections, with five appendices, covering the whole range of intensive care. All but two of the chapters have been written by the editors, which produces a very consistent approach.

The opening section provides an introduction to intensive care and includes an excellent chapter on severity scoring and outcome prediction. The subsequent sections cover the various systems of the body, with additional sections on infection, obstetrics, overdose, trauma and haematology.

The two "guest" chapters are on chest trauma and drowning and both maintain the standards set by the editors; indeed, the chapter on drowning by Dr Simcock is an excellent dissertation and should be compulsory reading for all trainees.

The appendices cover catheterization procedures, postoperative care of the cardiac surgery patient and procedures associated with organ donation. This last section is particularly well presented and will be of great value in clarifying the position for the new resident who is meeting this situation for the first time.

The editors have stated in their preface that the book is intended to fill a gap between large textbooks and brief reviews. They have achieved their intended goal with great success. This is an excellent short textbook of intensive care. It will be of great benefit to residents in the Intensive Care Unit, where it will provide useful guidelines at the bedside and, in addition, it will be an invaluable revision text for those preparing for postgraduate exams.

G. W. Jones

Conduction Blockade for Postoperative Analgesia: Mechanisms and Management. Edited by J. H. McClure and J. A. W. Wildsmith. Published by Edward Arnold, Sevenoaks. Pp. 230; indexed; illustrated.

There have recently been several new publications on postoperative pain relief, but there remains a place for a relatively short textbook dealing in depth with the role of local anaesthesia. In all respects, this book fits very nicely into the niche.

The book can be divided broadly into two sections: the pharmacology and physiology of postoperative pain treatment, and the practical aspects.

The first chapter by Cervero and Laird describes in detail the pathophysiology of pain pathways. It is an excellent up-to-date review which is difficult to criticize. It sets the scene very well for the remainder of the book and contains a particularly useful summary section. The next chapter, written by the late Ben Covino, considers the mechanisms of impulse block and reflects the true expertise of the author. It is written in a very clear and straightforward style and leaves the reader in no doubt as to the modern theories of action of the local anaesthetic agents. Neurotransmitters are clearly important in the function of pain pathways, and the next chapter considers the role of these in acute pain. Again, this is a good review, which in some respects is a logical progression from the previous chapter, but strays slightly from the purpose of the book.

As the recent report by the Royal Colleges of Anaesthetists and Surgeons makes clear, the most important reason for the treatment of postoperative pain is humanitarian. However, it is important to realize that pain has adverse effects on physiology and recovery after surgery, and the next chapter by N. B. Scott describes these. This is an awkward topic, but is covered well by the author. Again, this subject matter is a logical choice for a book of this nature, but it is not related solely to the local anaesthesia. A particular strength of this chapter is the large number of recent and well chosen references.

The remainder of the book concentrates on local anaesthetic techniques and the first chapter of this section, written by Brockway and Wildsmith, concerns intrathecal and extradural spread of drugs. The anatomy and physiology of the vertebral canal is described comprehensively and factors affecting extradural and intrathecal spread of drugs reviewed. The clinical use of spinal opioids is considered next by Morgan. Again, this is a well written and balanced review, which emphasizes the excellent analgesia that can be obtained by this method. However, the relatively high incidence of side effects is stressed, particularly respiratory depression. The relative safety of this technique compared with others is still not known for certain and he stresses the need for close monitoring of these patients. Very relevant to this last comment is the next chapter by Alfred Lee, describing the management of continuous extradural block. Management of these blocks in hospitals varies widely and it is difficult therefore to strike the correct balance in this chapter. However, the author succeeds well in giving a clear account of his subject and it is very useful indeed to those who are considering introducing extradural blocks for postoperative analgesia *de novo*.

Should a book such as this describe in great detail all known conduction blocks in anaesthetic practice? The editors have made a wise choice in describing only those procedures which are particularly suitable for providing prolonged postoperative analgesia. Thoracic and inguinal blocks and techniques for postoperative pain relief after upper and lower limb surgery are described by authors with considerable expertise in this area. Their descriptions are clear and there are many useful practical tips. In many cases, prior knowledge of the technique is assumed by the author. I believe that this is a fair and useful assumption to make, as most readers would either have seen these blocks performed or have access to a more detailed and comprehensive text.

The general layout of this small textbook is excellent. There are very many well drawn figures and the text is more than adequately referenced and indexed. I would recommend this book to all practising anaesthetists; it is a pleasure to read, and a genuine addition to the literature. If part of the function of the book is to persuade the reader to perform more local anaesthetic blocks for postoperative analgesia, then the authors have succeeded.

D. Rowbotham

Techniques in Extracorporeal Circulation, 3rd Edn. Edited by P. H. Kay. Published by Butterworth–Heinemann, Oxford. Pp. 336; indexed; illustrated. Price £95.00.

Considerable licence has been taken with the title of this book to create a compendium of modern technological aids to replace or supplement cardiac and pulmonary function. However, chapters on heart, heart–lung and lung transplantation appear incongruous, although they render the book comprehensive.

The bulk of the book comprises the many aspects of cardiopulmonary bypass and is rounded off with a set of reviews on ventricle assistance techniques, artificial hearts and respiratory gas exchange methods and devices. Each author has been given a wide brief, consequently there is much repetition of history and development, and many common themes. There is voice for designers, manufacturers and the users of cardiopulmonary bypass, but nothing from the mechanics. I feel that the perspective of a perfusionist would be valuable in reviewing their bibliography, safety measures and drills for the sudden appearance of blood clot in the reservoirs, air in the systems, and electromechanical failure.

Anaesthetists have contributed three chapters covering aspects of primes for perfusion, the cardiac anaesthetic process and intensive therapy. The first is too succinct. The second is a scratch golfer's guide to cardiac anaesthesia—straight down the fairway and no beating about the rough. The third misses an opportunity to wax lyrical on the use of chrono- and inotropes, vasodilators and constrictors with which to manipulate the post-bypass circulation; it gives no experience or imparted wisdom on interfacing patients to the technologies described in the later sections.

Some recent and current controversies are examined. The debate on neurological sequelae and complications is well aired and reaches conclusions. That on pulsatile versus non-pulsatile flow is founded and founders on evidence that is dated and based on bubble-oxygenator technology. Normothermic *vs* hypothermic bypass is broached, but is largely a subject that has arisen since the book was commissioned. What of pH *vs* alpha stat? They and it are not in the index.

With authors from both sides of the Atlantic, the usual criticisms can be levelled: there is a mixture of units of measurement, and one chapter is very difficult to read, containing malapropisms of almost presidential proportion. However, the book is really a treasure trove. To my mind, the crown jewels are chapters on filtration in bypass, intraoperative myocardial protection, neurological sequelae and intra-aortic balloon counterpulsation. They glitter, are lovingly cut, crafted, polished and assembled. There is gold also in chapters on haematology, renal failure, hypothermia and the newer technologies.

The literary line founded by Ionescue with the first edition is strong. This descendent is robust enough to maintain the health of the breed, and will probably increase in value, for it is the perfect time capsule of technology of cardiopulmonary surgery to herald the second millenium. I am tempted to hoard my copy and certainly will be circumspect with its loan or donation. I think it is a worthwhile purchase for anyone connected with this field and its fringes, for there is something of value in it for anaesthetists, surgeons, scientists or technicians, be it for interval reading, study or reference; and at a mere snip for a cardiac anaesthetist!

I. D. Conacher

Ward's Anaesthetic Equipment, 3rd Edn. By A. Davey, J. T. B. Moyle and C. S. Ward. Published by Harcourt-Brace-Jovanovich Ltd, Sidcup. Pp. 391; indexed; illustrated. Price £35.00.

This is the third edition of this textbook. Large parts of the second edition have been rewritten and revised and new material has been added. It has been revised with the needs of trainee anaesthetists in mind and the addition of two new co-authors has extended the scope of this edition. The principles that apply to the working of anaesthetic equipment and the safe use of this equipment are described.

In general, the book is well produced and illustrated. However, the medical cylinder data on the front inside cover are confusing, as the colour reproduction is poor. The bodies of the air and carbon dioxide cylinders appear green, when they should be grey.

The opening chapter covers physical principles; this has been expanded, with many useful and clear tables and graphs to explain the physical principles described. Pneumatics, fluidics and electronics are discussed in chapter 2, including brief descriptions of electronics and microprocessor systems; this is particularly relevant with the rapid expansion of microprocessor units in many types of anaesthetic monitoring equipment.

The chapter on the measurement of gas flow and volume is clear and instructive and the description of vaporizers has been updated and improved; working principles of vaporization are covered well, with many diagrams and photographs. The table of volatile anaesthetic agents should have included desflurane and sevoflurane in addition to the established agents.

Continuous flow anaesthetic machines are explained in a largely rewritten chapter, with the addition of many new photographs and diagrams. A short chapter on electronics in the anaesthetic machine has been added.

Breathing systems and their components are comprehensively covered, with descriptions of all major breathing systems, including the Humphrey ADE system. The description of the circle system has been extended and updated, with discussion of the vapour and gas concentrations produced within the system. Some parts of this chapter, particularly the descriptions of breathing attachments and face masks, remain unaltered from previous editions and have a rather old feel to them, but despite this remain useful. The description of tracheal tubes has been revised and now includes examples of the commonly used plastic tubes. The frequently used RAE tube for ENT anaesthesia is not described, and the laryngeal mask airway that has become a major influence on British anaesthetic practice over the past 5 years merits only a short description.

The chapter on resuscitation and automatic ventilators has been largely rewritten. Ventilators have been classified according to whether they are low- or high-powered and then according to the method used for cycling. The classification is then continued to cover function—mechanical thumbs, minute volume dividers and bag squeezers. Many machines are described in detail, ranging from the Cape Waine and the East Radcliffe ventilators to the Servo 900D. Description of jet ventilators has been expanded and includes a section on the Penlon Bromsgrove jet ventilator.

Chapter 14 provides an overview of the equipment used for paediatric anaesthesia; many new diagrams and photographs have been added and these are clear and instructive.

Monitoring is divided into two parts: measurement of gases used in anaesthesia and non-invasive patient monitoring. To take account of the many developments in infusion technology both in the intensive care unit and in theatre, a chapter on the basic components of infusion equipment has been added. The chapter on the psychology of accidents was both interesting and relevant.

Overall, this book has been improved considerably and updated to take account of the changes in anaesthetic practice that have occurred in the 7 years since the previous edition. This book should certainly find a place in all departmental libraries. Trainee anaesthetists preparing for the F.R.C.Anaes. examination will find it a valuable source of information and I am sure that many anaesthetists will want to add this book to their own personal library.

J. A. Langton

ERRATUM

British Journal of Anaesthesia 1992; **69**: 546

As a result of a typesetting error and proof-reading oversight, the dates of reading material suggested by the authors of the book *MCQ for the Higher Examination in Clinical Pharmacology* were incorrectly printed as 1980–1981, instead of 1980–1991, in the review by Dr W. S. Nimmo. We apologise both to the authors, Drs G. McCarthy and R. K. Mirakhur, and to Dr Nimmo, for any embarrassment caused to them.

Papers for publication and all editorial communications should be addressed to the Editor, University Department of Anaesthesia, Leicester Royal Infirmary, Leicester LE1 5WW; business communications to the Publishers: Professional & Scientific Publications Ltd, BMA House, Tavistock Square, London WC1H 9JR.

The GUIDE TO CONTRIBUTORS may be found in the advertisement section of this issue (pages ii, iv & vi).
Published monthly. Annual subscriptions: Worldwide £125.00; USA only $198.00 (direct orders only). Trainee rate: Worldwide £69.00. Airmail rates on application. ISSN 0007–0912. Orders must be accompanied by payment; cheques should be made payable to Professional and Scientific Publications. Orders and payments should be sent to Professional and Scientific Publications, BMA House, Tavistock Square, London WC1H 9JR. Orders in the United States of America may be sent to Professional and Scientific Publications, Box 560B, Kennebunkport, Maine 04046.

Group Advertisement Director, Mr R. Hayzen.
Advertisement Manager, Mr A. Allsop.
Publishing Manager, Mr D. Shaw.
BMA House, Tavistock Square, London WC1H 9JR. 071-387 4499.

Whilst every effort is made by the publishers and editorial committee to see that no inaccurate or misleading data, opinions or statement appears in this Journal, they wish to make it clear that the data and opinions appearing in the articles and advertisements herein are the responsibility of the contributor or advertiser concerned. Accordingly, the publishers and the editorial committee and their respective employees, officers and agents accept no liability whatsoever for the consequences of any such inaccurate or misleading data, opinions or statement. Whilst every effort is made to ensure that drug doses and other quantities are presented accurately, readers are advised that new methods and techniques involving drug usage, and described within this Journal, should only be followed in conjunction with the drug manufacturer's own published literature.

© Copyright: 1993 *British Journal of Anaesthesia*
All rights reserved. No part of this publication may be reproduced, stored in a retrieval system, or transmitted in any form by any means, electronic, mechanical, photocopying, recording or otherwise, without the prior permission of the *British Journal of Anaesthesia.*

Published by Professional and Scientific Publications.
Printed in Great Britain by the University Press, Cambridge.

"*I would have everie man write what he knowes and no more.*"—MONTAIGNE

BRITISH JOURNAL OF ANAESTHESIA

VOLUME 70, No. 4 APRIL 1993

EDITORIAL

EXTRADURAL ABSCESS AFTER CENTRAL NEURAL BLOCK

Major sequelae, such as paraplegia and the formation of a haematoma or abscess in the vertebral canal, are extremely rare after central neural block. Because of that rarity it is essential that every case is examined in detail to see what lessons there are for others, so that the future risk of such disasters is minimized. This issue of *British Journal of Anaesthesia* contains a report of an extradural abscess that occurred in a patient who had received multiple injections of both local anaesthetic and corticosteroid drugs in the management of a chronic pain syndrome [1].

In describing this patient and referencing *selectively* a number of others from the relatively recent literature, Bromage draws our attention to the problem associated with the interval between procedure and appearance of the early symptoms and signs. This interval may be so long that not even the patient associates new developments with the previous injection, the problem being compounded if presentation is at a hospital without a record of that procedure. The index of suspicion is thus low and damage to the spinal cord or cauda equina may be irreversible before the correct diagnosis is made. It is proposed that this delay could be minimized, or even averted, if patients wear "Medic-Alert" bracelets for a period of time after performance of the block. However attractive the proposal may be at first sight, it is important to recognize that there is much that we do not know about the condition. Extradural abscess occurs sporadically in the normal population and there are no good data on its incidence, with or without prior instrumentation of the vertebral canal. There is no clear evidence to suggest a cause and effect relationship, although it is difficult to argue against this when there is a temporal connection [2]. It may also be difficult, with the benefit of hindsight, to accept or understand any delay in diagnosis, but the evidence presented indicates clearly that such delay can occur.

Against this background, it is interesting to examine the new case he describes. The first point is that the patient would appear to have received extradural injections at the mid-thoracic level, yet the abscess formed in the lower cervical region and caused a quadraplegia. Was it related to the injection? Second, it was 10 days after the last injection before persistent symptoms developed. Does it take this long for an abscess to form? Perhaps though, the relative "trauma" of the journey the patient undertook 1 week after the last injection produced a haematoma within the vertebral canal, the contents of which had been made friable by repeated injections of steroids. Such a haematoma might then have become infected and produced an abscess within 2–3 days. The final concern is that conservative treatment was continued for 4 days after a consultant neurologist made a tentative diagnosis of extradural abscess. This condition, in common with extradural haematoma, is a medical emergency that requires early diagnosis and rapid management or permanent paralysis may result, as was sadly the case here.

One would wish that a full history had elicited the background of extradural injections for a chronic pain syndrome, particularly because the patient again presented with back pain. However, the other cases that Bromage cites show that a failure to make such a connection is not an isolated occurrence. He argues that some way of heightening awareness among subsequent medical attendants is needed and thus proposes a mandatory warning system in the form of the Medic-Alert bracelet. He recognizes that there are both financial and medico–legal implications, although he makes no mention of the cost of providing a bracelet to each patient (currently £30). In the U.K. alone, many thousands of patients receive a subarachnoid or extradural injection each year and implementation would be expensive, in addition to generating significant paperwork. It would surely produce considerable patient anxiety about a complication that the great majority of anaesthetists (including frequent users of central neural block) may never see.

To disagree with the proposal does not imply that one can ignore the concerns that led Bromage to his conclusion, but a more measured approach is needed. First, we should never lose sight of the infective complications associated with our anaesthetic techniques and thus use a meticulous aseptic technique and aim to minimize local trauma. Central nerve blocks breach the very significant protection that nature provides for the central nervous system and this should never be done lightly.

Second, we need information on the incidence of extradural abscess and this requires collection of epidemiological data that include an accurate record of the number of central nerve blocks performed each year in large populations. The increasing requirement for medical audit suggests that such data may be collected more readily in future than they have been in the past. I accept that we need also to raise the index of suspicion among both patients and physicians when a patient presents with back pain sometime after a block. The difficulty in making any recommendation is that it should be based on assessment of the risk and this we do not have, and of course any recommendation has to be related to the medico–legal climate in each country. Even a manoeuvre as simple as telling the patient to remember they have received a "spinal" injection if they develop any back symptoms in the succeeding month or two may cause untold difficulties. Until we have better information, I believe that any change from current practice is almost bound to be counterproductive.

J. A. W. Wildsmith
Edinburgh

ACKNOWLEDGEMENT

I thank Dr D. G. Littlewood for kindly reviewing this script.

REFERENCE

1. Bromage PR. Spinal extradural abscess: pursuit of vigilance. *British Journal of Anaesthesia* 1993; **70**: 471–473.
2. Ngan Kee WD, Jones MR, Thomas P, Worth RJ. Extradural abscess complicating extradural anaesthesia for Caesarean section. *British Journal of Anaesthesia* 1992; **69**: 647–652.

British Journal of Anaesthesia 1993; **70**: 389–393

ORIGINAL ARTICLES

CLOSED-LOOP FEEDBACK CONTROLLED ADMINISTRATION OF ALFENTANIL DURING ALFENTANIL–NITROUS OXIDE ANAESTHESIA

H. SCHWILDEN AND H. STOECKEL

SUMMARY

We have studied the automatic administration of alfentanil during alfentanil–nitrous oxide anaesthesia in 11 patients using a closed-loop feedback control system based on EEG analysis. We chose a median EEG frequency of 2–4 Hz as the EEG set point. The slope of the asymptote to the cumulative dose requirement was used to define an effective therapeutic infusion of alfentanil. Median EEG frequency (mean (SD)) during the feedback period was 3.03 (0.45) Hz. The average effective therapeutic infusion of alfentanil was 0.140 (0.032) mg min^{-1}. We conclude that EEG feedback control may be useful in assessing and defining the dose requirements of alfentanil. (Br. J. Anaesth. 1993; **70**: 389–393)

KEY WORDS

Anaesthetic techniques: intravenous infusion, closed-loop feedback control. Analgesics: alfentanil. Brain: electroencephalogram.

In general, the continuous administration of alfentanil for maintaining general anaesthesia is supplemented by nitrous oxide, volatile or i.v. anaesthetic agents. Various methods have been used for identifying the appropriate rate of infusion to maintain an adequate level of anaesthesia. Prys-Roberts and colleagues [1] proposed the term minimal infusion rate (MIR) as that rate of infusion at which 50 % of the patients do not respond to skin incision. MIR may be considered as a systematic approach to both establishing relative potencies and providing guidelines on dosage requirements. However, by definition it requires a response to skin incision. It has been suggested that a more useful approach would be for the anaesthetist to know the rate of administration which was successful, for instance, in 95 % of patients. A potential method of defining this rate of infusion may be the use of closed-loop feedback controlled drug delivery systems.

Alfentanil decreases EEG frequency in a concentration-dependent manner [2]. The aim of this study was to identify, during alfentanil–nitrous oxide anaesthesia, the rate of infusion of alfentanil necessary to maintain a given slowing of EEG frequency.

PATIENTS AND METHODS

After obtaining institutional Ethics Committee approval and informed written consent, we studied 11 patients (ASA I, II) undergoing general surgery (table I). Premedication consisted of pethidine 50 mg and promethazine 50 mg i.m. given 45 min before anaesthesia. Anaesthesia was induced with fentanyl 0.1 mg and thiopentone 300–500 mg, followed by suxamethonium 80 mg. The trachea was intubated and the lungs ventilated with 60 % nitrous oxide in oxygen for the duration of surgery. Neuromuscular block was maintained by administration of either repetitive bolus doses of pancuronium or continuous infusion of vecuronium to maintain a 90 % reduction in twitch response to a train-of-four stimulus. Patient monitoring consisted of ECG, automatic non-invasive arterial pressure (Dinamap) and end-tidal $P\text{CO}_2$ ($P\text{E}'_{\text{CO}_2}$) (Hewlett–Packard 47210A). Artificial ventilation was adjusted to maintain $P\text{E}'_{\text{CO}_2}$ at 4.5 kPa. Immediately before skin incision, a bolus of alfentanil 3 mg was given and the feedback control system for the administration of alfentanil activated. Alfentanil was administered via an indwelling cannula in the forearm by an infusion pump (Treonic, Vickers) which was interfaced to a computer (Eltec, Eurocom). During surgery, no other anaesthetic medication was administered.

EEG analysis

Four EEG leads (Cz-Fi, Cz-Oi; i = 1,2) were amplified (Mingograph Junior, Siemens) and recorded on magnetic tape (PR 2200 Ampex). The Cz-Oi lead having the smaller impedance was used for deriving the feedback signal.

The filter settings of the EEG amplifier were 0.3 s and 70 Hz. Before A–D conversion, the signal was analogue filtered between 0.5 and 32 Hz, divided into epochs of 8.192 s and digitized at a rate of 125 Hz with 12 bit A–D resolution. Median EEG frequency of EEG power spectrum was used as feedback signal. We chose the interval 2–4 Hz as the set point for maintenance of anaesthesia [3, 4]. As the administration algorithm, we used a procedure described earlier [5–7]. This algorithm used an integrated pharmacokinetic–pharmacodynamic model to calculate the infusion strategy to set and maintain the desired effect. If measured median

---

HELMUT SCHWILDEN, M.D., PH.D., HORST STOECKEL, M.D., F.R.C.ANAES.; Institut für Anästhesiologie, Rheinische Friedrich-Wilhelms-Universität, Universität Bonn, Sigmund-Freud-Str. 25, D-5300 Bonn 1, Germany. Accepted for Publication: October 26, 1992.

TABLE I. *Patient characteristics and type of surgery*

Patient	Sex	Age (yr)	Height (cm)	Weight (kg)	Surgery
1	M	39	168	65	Gastrectomy
2	F	50	168	70	Plastic, necrosis foreleg
3	F	53	168	70	Reduction of mamma
4	M	63	176	90	Amputation of rectum
5	M	38	175	60	Resection of small intestine
6	M	60	178	90	Resection of rectum
7	M	52	175	60	Resection of sigmoid colon
8	M	43	186	75	Gastrectomy
9	F	55	154	61	Resection of rectum
10	M	63	167	70	Resection of sigmoid colon
11	M	59	180	84	Resection of sigmoid colon
Mean		52.3	172.3	72.3	
SD			8.5	11.3	

EEG frequency was different from the model prediction, the model parameters were adapted appropriately. If measured median EEG frequency was outside the desired range, a new infusion strategy was derived from the adapted model to match the set point. This cycle was performed every 8.192 s.

Definition of effective therapeutic infusions

Under the condition of linear pharmacokinetics, the amount of drug administered per unit time $I(t)$ and the resulting concentration $C(t)$ is given by:

$$C(t) = \int_0^t dt' G(t-t') I(t')$$

The disposition function $G(t)$ can be modelled for alfentanil by a biexponential function [8]:

$$G(t) = A \exp(-\alpha t) + B \exp(-\beta t)$$

Assuming that the maintenance of a constant effect, E, is associated with a constant concentration, C, it can be shown [9] that the cumulative amount $D(t) = \int_0^t dt' I(t')$ to maintain E has the general form:

$$D(t) = M_1 - M_2 \exp(-kt) + I_{ss} t$$

The asymptote of the cumulative dose requirement curve, $D(t)$, is given by the function $M_1 + I_{ss} t$, where the unit I_{ss} obviously defines the slope of the asymptote. Given a feedback system which maintains a certain effect within the therapeutic window, the asymptote I_{ss} to the emerging cumulative dose curve, $D(t)$, defines an effective therapeutic infusion [7, 10]. In this study, we used non-linear least square fitting to determine I_{ss} from the foregoing formulae as an estimate of the effective therapeutic infusion of alfentanil.

RESULTS

Table II summarizes the findings of quantitative EEG analysis. According to the desired set point of median EEG frequency of 2–4 Hz, the median EEG frequency varied between individuals in the range 2.2–3.6 Hz with a mean of 3.03 (SD 0.45) Hz. As can be identified from the resolution of the power spectrum into frequency bands, EEG slowing was caused largely by a frequency shift into the frequency band of 0.5–2 Hz which contained on average 40% of total EEG power. Edge frequency (95% percentile of EEG power spectrum) was found to be 15.4 (3.1) Hz.

Figure 1 depicts the typical time course of cumulative alfentanil requirement for a typical patient (No. 1) whose effective therapeutic infusion rate was assessed as 0.14 mg min^{-1}. Figure 2 shows the time course of mean (SD) cumulative alfentanil requirement for all 11 patients for the first 120 min. The average cumulative amount for the first 120 min was 23.5 mg. Table III depicts the behaviour of arterial pressure and heart rate before anaesthesia, after skin incision and at the end of surgery and the corresponding values at greatest systolic and least diastolic arterial pressure measured during surgery. Table IV gives the individual effective therapeutic infusions for the 11 patients whose alfentanil requirements varied between 0.108 and 0.22 mg min^{-1}, and the duration of surgery and recovery time from end of surgery to opening eyes on command.

We were unable to identify a significant relationship between effective therapeutic infusion and body mass or lean body mass. None of the patients had

TABLE II. *Analysis of EEG power spectrum. Edge frequency refers to 95% percentile, median indicates the 50% quantile of EEG power spectrum. Individual values represent the time average over the surgical period*

	Proportion of EEG power (%)							
Patient	0.5–2 Hz	2–5 Hz	5–8 Hz	8–13 Hz	13–32 Hz	Median (Hz)	Edge freq. (Hz)	Amplitude (μV)
1	37.95	22.53	24.13	8.65	6.74	3.27	14.36	10.46
2	41.84	15.56	10.79	26.48	5.32	3.30	13.11	11.83
3	36.86	24.95	10.17	14.34	13.69	3.55	16.78	12.31
4	36.28	30.28	8.47	8.21	16.77	2.93	20.60	6.64
5	40.71	25.27	22.62	7.24	4.17	2.91	12.68	16.71
6	42.90	37.97	11.36	3.98	3.78	2.27	10.53	9.21
7	46.25	14.48	10.58	18.64	10.05	2.93	15.31	12.49
8	47.05	23.25	15.40	9.43	4.87	2.22	12.58	9.59
9	35.52	25.53	10.59	16.91	11.44	3.61	16.24	10.24
10	40.16	23.32	8.14	9.92	18.46	3.12	19.73	9.33
11	40.79	19.16	9.52	16.81	13.71	3.20	17.62	11.82
Mean	40.57	23.85	12.89	12.78	9.91	3.03	15.41	10.97
SD	3.82	6.54	5.53	6.51	5.28	0.45	3.14	2.56

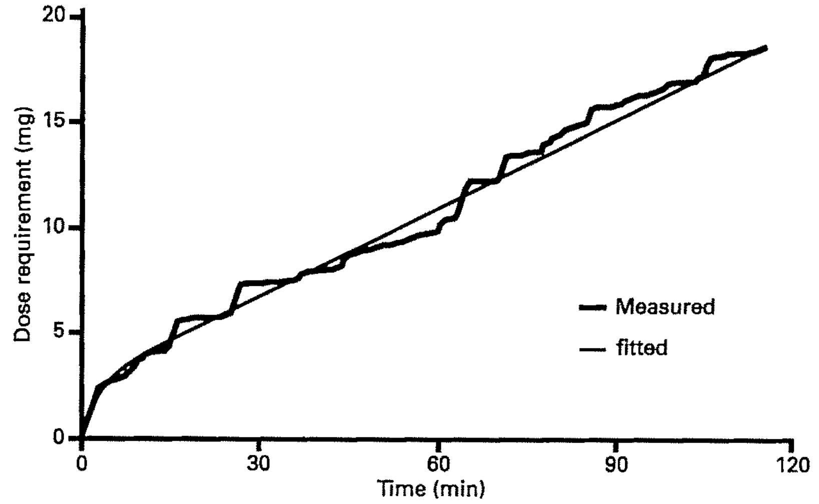


FIG. 1. Example of a cumulative dose requirement curve (patient No. 1) of alfentanil during feedback control maintaining a median EEG frequency of 2–4 Hz.

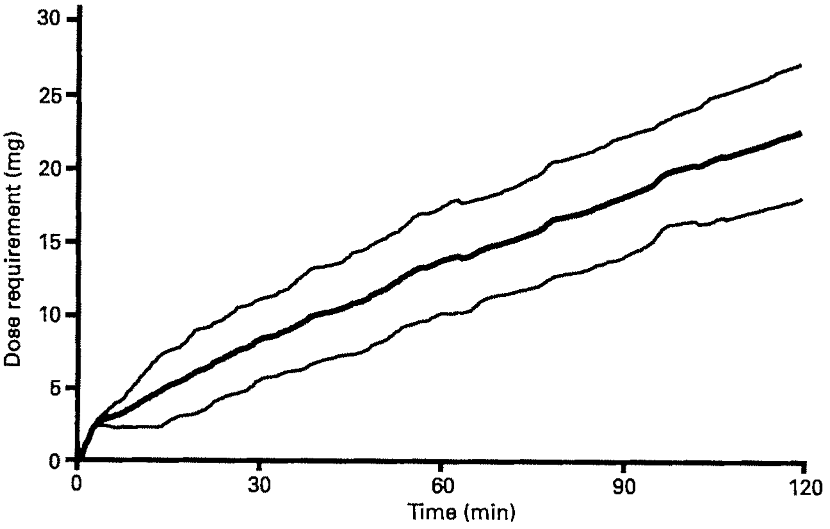


FIG. 2. Average cumulative dose requirement curve (mean, SD) of alfentanil in 11 patients during feedback control maintaining a median EEG frequency of 2–4 Hz.

TABLE III. *Systolic and diastolic arterial pressures (AP) (mm Hg) and heart rate (HR) (beat min^{-1}) before induction of anaesthesia and during surgery. Greatest SAP and Least DAP refer to values recorded during surgery*

	Preanaesthetic		Skin incision		End surgery		Greatest SAP		Least DAP	
Patient	AP	HR	AP	HR	AP	HR	AP	HR	AP	HR
1	140/85	78	105/60	56	120/75	65	150/90	58	105/60	56
2	125/80	80	125/75	68	130/70	70	165/95	75	105/65	58
3	130/85	60	115/70	54	105/60	50	125/80	55	105/55	55
4	130/70	75	145/80	68	115/65	77	160/90	68	90/60	60
5	115/75	72	120/75	57	115/75	52	145/85	58	125/70	62
6	170/90	115	120/75	62	110/75	83	175/105	95	90/50	105
7	115/75	65	125/80	58	110/65	65	150/85	70	105/60	60
8	140/80	57	150/90	57	125/75	80	180/115	70	115/75	62
9	160/90	110	105/60	63	110/60	62	140/90	80	90/50	65
10	150/80	70	110/70	60	115/70	62	130/85	58	110/60	59
11	130/75	75	90/60	57	110/75	63	120/70	77	80/40	65

TABLE IV. *Individual effective therapeutic infusions (ETI) for alfentanil as determined from the asymptote to the cumulative dose requirement curve, duration of surgery and recovery times from end of surgery to open eyes on command*

Patient	ETI (mg min^{-1})	Duration of surgery (min)	Recovery time (min)
1	0.139	200	19
2	0.217	75	7
3	0.135	105	17
4	0.108	255	6
5	0.113	125	14
6	0.121	120	13
7	0.122	125	20
8	0.165	190	20
9	0.163	130	31
10	0.134	155	22
11	0.121	170	35
Mean	0.140	150.0	18.5
SD	0.032	50.7	8.9

recall of intraoperative events on explicit questioning either immediately after extubation or 24 h after surgery.

DISCUSSION

We have demonstrated the use of EEG-driven automated feedback controlled delivery of alfentanil during alfentanil–nitrous oxide anaesthesia during surgery. Several years ago, on the basis of pharmacokinetic investigations and clinical experience [11, 12], our group proposed a target concentration of alfentanil 400–500 ng ml^{-1} during anaesthesia with 60% nitrous oxide for major surgery. Given the pharmacokinetic data of Schüttler and Stoeckel [8], this concentration corresponds to a maintenance infusion rate of approximately 0.14 mg min^{-1} for adult patients. Subsequently, several authors have undertaken studies to determine appropriate dose requirements for alfentanil, mostly in combination with 66% nitrous oxide. They usually used arterial pressure and heart rate for defining additional alfentanil requirements. Ausems, Hug and de Lange [13] reported an average rate of infusion of alfentanil 1.72 (0.15) μg kg^{-1} min^{-1} (with 66% nitrous oxide) during intra-abdominal surgery (corresponding to 0.123 (0.011) mg min^{-1} for a patient of 72 kg body weight). Lemmens and colleagues [14] reported, in a group of 18 elderly patients (65–86 yr; average body weight 67 kg), a total requirement of alfentanil 23.5 (10.7) mg for an average duration of anaesthesia of 162 (42) min (with 66% nitrous oxide); this corresponded to an infusion rate of 0.156 mg min^{-1}. Gesink-van der Veer and colleagues [15] found, in patients with Crohn's disease and of average weight 55.8 kg, a mean infusion rate of 2.1 μg kg^{-1} min^{-1} and, in a control group of average weight 64.4 kg, a mean rate of 1.05 μg kg^{-1} min^{-1}; these correspond to infusion rates of 0.151 mg min^{-1} and 0.076 mg min^{-1} for a 72-kg patient in each group, respectively.

A later study by Ausems and colleagues [16] found that an average rate of infusion of 1.43 (0.55) μg kg^{-1} min^{-1} for lower abdominal surgery and 1.99 (0.55) μg kg^{-1} min^{-1} for upper abdominal surgery (with 66% nitrous oxide) was necessary to avoid "response" as defined by a set of criteria reflecting haemodynamic and autonomic changes. These data correspond to infusion rates of 0.1 (0.04) mg min^{-1} and 0.14 (0.04) mg min^{-1} for a 72-kg patient. Comparison of these data with our study suggests that median EEG frequency may serve as an alternative guide to define appropriate doses of alfentanil during alfentanil–nitrous oxide anaesthesia. Obviously, our data do not allow us to conclude that our mode of administration is superior to repetitive bolus dosing or other infusion techniques. This requires further investigation.

This study and previous ones [5–7] confirm that feedback controlled drug delivery systems have the potential both to provide clinical anaesthesia and to serve as experimental research tools. Unlike MAC or MIR values, which use quantal responses and cannot define optimum values for achieving anaesthesia in the majority of patients, the effective therapeutic infusion concept uses a therapeutic end-point for evaluating dose requirements. The method determines not only what dose is effective in a given quantile, but also the dose that is effective in all patients.

ACKNOWLEDGEMENT

This work was supported in part by a grant from the Ministerium für Wissenschaft and Forschung, NRW, Federal Republic of Germany.

REFERENCES

1. Prys-Roberts C, Davies JR, Calverley RK, Goodman NW. Haemodynamic effects of infusions of diisopropyl phenol (ICI 35868) during nitrous oxide anaesthesia in man. *British Journal of Anaesthesia* 1983; **55**: 105–111.
2. Scott JC, Ponganis KV, Stanski DR. EEG quantitation of narcotic effect. The comparative pharmacodynamics of fentanyl and alfentanil. *Anesthesiology* 1985; **62**: 234–241.
3. Desiderio DP, Thorne AC. Awareness and general anaesthesia. *Acta Anaesthesiologica Scandinavica* 1990; **34** (Suppl. 92): 45–50.
4. Schwilden H. Use of the median EEG frequency and pharmacokinetics in determining depth of anaesthesia. In: Jones JG, ed. *Baillières Clinical Anaesthesiology*. London: Baillière–Tindall 1989; 603–622.
5. Schwilden H, Schüttler J, Stoeckel H. Closed-loop feedback control of methohexitone anaesthesia by quantitative EEG-analysis in humans. *Anesthesiology* 1987; **67**: 53–59.
6. Schwilden H, Stoeckel H, Schüttler J. Closed-loop feedback control of propofol anaesthesia by quantitative EEG analysis in humans. *British Journal of Anaesthesia* 1989; **62**: 290–296.
7. Schwilden H, Stoeckel H. Effective therapeutic infusions produced by closed-loop feedback control of methohexital administration during total intravenous anesthesia with fentanyl. *Anesthesiology* 1990; **73**: 225–229.
8. Schüttler J, Stoeckel H. Alfentanil (R 39209) Ein neues kurzwirkendes Opioid. Pharmakokinetik and erste klinische Erfahrungen. *Anaesthesist* 1982; **31**: 10–14.
9. Keeri-Szanto M. Anesthetic time/dose curves. The limiting factor in the utilization of intravenous anesthetics during surgical operations. *Clinical Pharmacology and Therapeutics* 1961; **2**: 45–51.
10. Schwilden H, Schüttler J. Bestimmung effektiver therapeutischer Infusionsraten (ETI) für intravenöse Anaesthetika durch feedback-geregelte Dosierung. *Anaesthesist* 1990; **39**: 603–606.

11. Schüttler J, Stoeckel H, Schwilden H, Lauven PM. Pharmakokinetisch begründete Infusionsmodelle für die Narkoseführung mit Alfentanil. In: Doenicke A, ed. *Alfentanil.* Berlin, Heidelberg, New York: Springer, 1986; 42–51.
12. Stoeckel H, Schüttler J, Schwilden H. Grundlagen der Infusionsnarkose mit Alfentanil. In: Zindler M, Hartung E, eds. *Alfentanil. Ein neues, ultrakurzwirkendes Opioid.* München–Wien–Baltimore: Urban & Schwarzenberg, 1985; 141–150.
13. Ausems EM, Hug CC, de Lange S. Variable rate infusion of alfentanil to nitrous oxide anesthesia for general surgery. *Anesthesia and Analgesia* 1983; 62: 982–986.
14. Lemmens HJM, Burm AGL, Bovill JG, Hennis PJ. Pharmacodynamics of alfentanil as a supplement to nitrous oxide anaesthesia in the elderly. *British Journal of Anaesthesia* 1988; 61: 173–179.
15. Gesink-van der Veer BJ, Burm AGL, Hennis PJ, Bovill JG. Alfentanil requirement in Crohn's disease. *Anaesthesia* 1989; 44: 209–211.
16. Ausems EM, Hug CC, Stanski DR, Burm AGL. Plasma concentrations of alfentanil required to supplement nitrous oxide anaesthesia for general surgery. *Anesthesiology* 1986; 65: 362–373.

British Journal of Anaesthesia 1993; 70: 394–396

COMPARISON OF THE EFFECT OF EMLA CREAM, SUBCUTANEOUS RING ANAESTHESIA AND A DOUBLE CUFF TECHNIQUE IN THE PREVENTION OF TOURNIQUET PAIN

Y.-C. TSAI, Y.-Y. LAI AND C.-L. CHANG

SUMMARY

*We have examined the effect of EMLA on tourniquet pain and compared it with those of subcutaneous ring anaesthesia (SRA), a double cuff technique and a single cuff (control) during i.v. regional anaesthesia. The durations of analgesia (mean 57.3 (*SD *16.6) min) and tolerance (72.3 (13.9) min) to tourniquet inflation in the EMLA group were comparable to those in the SRA group (54.1(16.2) min and 68.3(19.0) min), but significantly (*$P < 0.05$*) greater than those in the control group (30.0 (10.7) min and 45.6 (14.0) min). The double cuff technique was the most effective method, with 91.5 (14.9) min duration of analgesia. We conclude that EMLA provided a significant analgesic effect on tourniquet pain compared with the control group, but a relatively limited analgesic effect compared with a double cuff technique.* (Br. J. Anaesth. 1993; **70**: 394–396)

KEY WORDS

Anaesthetic techniques: intravenous regional. Anaesthetics local: topical lignocaine/prilocaine. Complications: tourniquet pain.

I.v. regional anaesthesia (IVRA) is a useful and safe block for analgesia of the extremities. Nevertheless, analgesia at the site of the tourniquet is not achieved as easily as that at the operative site and various methods have been described to relieve tourniquet pain [1–5]. EMLA (Astra), a 5 % eutectic mixture of two local anaesthetics, lignocaine and prilocaine, has been shown to be effective in producing local anaesthesia of intact skin in infants, children and adults [6–11]. The purpose of this study was to evaluate the effect of EMLA in the prevention of tourniquet pain, and compare it with subcutaneous ring anaesthesia (SRA), a double cuff technique and a standard technique (control).

PATIENTS AND METHODS

This study was performed in a randomized, single-blind, controlled manner and was approved by the local Ethics Committee. Informed consent was obtained from each patient. Forty adult patients (ASA physical status I or II) undergoing elective forearm or hand surgery were allocated randomly to four groups of 10. No premedication was given. With the patient supine, an i.v. cannula was placed in a vein on the dorsum of the hand or distal forearm of the limb to be blocked. The tourniquet, 6.5 cm in width, was applied midway between axilla and elbow over a cushioning layer of orthopaedic padding. Before IVRA, patients in group 1 received topically applied 5 % EMLA cream 30–35 g circumferentially over the site of the tourniquet, then an occlusive plastic dressing was positioned for 1 h. Patients in group 2 received SRA with 1 % lignocaine 20 ml, using a 22-gauge, 70-mm long needle at the site of tourniquet just before the single pneumatic tourniquet cuff was applied; the total dose of lignocaine combined with that used in IVRA was 400 mg. Double tourniquet cuffs (6 cm wide) were used in group 3 patients, without EMLA or SRA. The proximal cuff was inflated to 250 mm Hg after the arm was exsanguinated with an Esmarch bandage. The distal cuff was inflated and the proximal cuff released 30 min after i.v. injection of lignocaine. Patients in group 4 (control group) received placebo cream (a cream base containing no local anaesthetic) over the site of tourniquet, using the same procedure as in group 1. For each patient, the arm was exsanguinated by applying an Esmarch bandage from the finger tips to the tourniquet site. The cuff was inflated to 250 mm Hg. When satisfactory ischaemic conditions were obtained, the solution of 0.5 % lignocaine 40 ml was injected.

The duration of tourniquet analgesia was defined as the time between application of tourniquet pressure and complaint of tolerable pain or soreness over the tourniquet site. The duration of tourniquet tolerance was defined as the time between application of tourniquet pressure and complaint of intolerable pain or discomfort that required additional analgesia.

Data were analysed by Kruskal–Wallis test with Dunn procedure. P less than 0.05 was considered statistically significant.

RESULTS

Patient characteristics are shown in table I. The duration of analgesia to tourniquet inflation was regarded as the same as the duration of operation (which lasted longer than 90 min) if the patient still

---

YU-CHUAN TSAI, M.D.; YUH-YEONG LAI, M.D.; CHUAN-LIN CHANG, M.D.; Department of Anaesthesiology, National Cheng Kung University Hospital, 138 Shing-Li Rd, Tainan 70428, Taiwan R.O.C. Accepted for Publication: October 19, 1992.

Correspondence to Y.-C.T.

TABLE I. *Patient data (mean (range or SD))*

	EMLA ($n = 10$)	SRA ($n = 10$)	Double cuff ($n = 10$)	Control ($n = 10$)
Age (yr)	32.6 (17–63)	36.8 (22–60)	35.6 (22–61)	37.7 (26–65)
Sex (M/F)	6/4	4/6	5/5	5/5
Weight (kg)	61.6 (11.5)	59.3 (7.8)	61.1 (10.0)	56.9 (9.6)
Height (cm)	163.6 (7.7)	163.9 (8.2)	164.3 (5.4)	161.3 (10.5)

TABLE II. *Mean (SD) durations of analgesia and tolerance to tourniquet inflation in each group. $P < 0.05$: * compared with other three groups ; † compared with control group. CI = confidence interval*

	EMLA ($n = 10$)	SRA ($n = 10$)	Double cuff ($n = 10$)	Control ($n = 10$)
Duration of analgesia (min)	57.3 (16.6)†	54.1 (16.2)	91.5 (14.9)*	30.0 (10.7)
95% CI	(45.4–69.2)	(42.5–65.7)	(80.8–102.2)	(22.3–37.7)
Duration of tolerance (min)	72.3 (13.9)†	68.3 (19.0)	—	45.6 (14.0)
95% CI	(62.4–82.2)	(54.7–81.9)	—	(35.6–55.6)

had no complaint about the tourniquet site. The mean duration of analgesia to tourniquet inflation in the double cuff group was 91.5 (SD 14.9) min, which was significantly longer than that in the SRA, EMLA or control groups ($P < 0.05$) (table II). The mean duration of analgesia to tourniquet inflation in the EMLA group was 57.3 (16.6) min, comparable to that in the SRA group (54.1(16.2) min) ($P < 0.05$ compared with the control group (30.0 (10.7) min). The duration of tolerance to tourniquet inflation in the double cuff group could not be evaluated for lack of data in eight of 10 patients because surgery ended before occurrence of intolerable symptoms. The mean duration of tolerance to tourniquet inflation in the EMLA group (72.3 (13.9) min) was not significantly different from that in the SRA group (68.3 (19.0) min), but was significantly longer ($P < 0.05$) compared with the control group (45.6 (14.0) min).

DISCUSSION

To avoid subjectively reminding patients about their tourniquet pain, we did not evaluate pain scores at fixed intervals, but for practical purposes, we selected two points to evaluate pain, the duration of tourniquet analgesia and the duration of tourniquet tolerance. These two points were equivalent to each end of a visual analogue scale (perceptible and intolerable). Our study indicated that the duration of tourniquet analgesia and duration of tourniquet tolerance in the EMLA group were significantly longer compared with the control group. Lowrie, Jones and Eastley [12], studying 10 healthy male volunteers, found a significantly longer duration and smaller pain scores in an EMLA group. However, the duration of tourniquet analgesia or tolerance in the EMLA group is of little clinical significance, because the technique is time-consuming, variably effective and expensive. We found that the most reliable method was the double cuff technique.

Although the double cuff is not favoured by some users because of the increased incidence of tourniquet failure in IVRA [13, 14], this technique is both effective and safe in the prevention of tourniquet pain if used correctly and carefully. Brown, McGriff and Malinowski reviewed 1906 cases receiving IVRA with a double tourniquet and concluded that the major cause of adverse effects was technical error [15]. It is essential that all equipment be checked before use. However, it is held by many clinicians that the double cuff method is less safe than a single cuff technique. Using EMLA cream or SRA to prevent tourniquet pain with a single cuff technique may be an alternative, but not ideal, method in clinical practice.

Subcutaneous ring anaesthesia was reported by Rousso and colleagues to be an excellent analgesic technique for tourniquets [2]. However, in our study, SRA only provided similar analgesia as EMLA. Lack of a control group and the duration of observation in Rousso's study may explain the difference in observations. Although there were no toxic signs in the SRA group patients who received lignocaine 400 mg (half in SRA and half in IVRA), the total dose was significantly in excess of the maximal recommended doses. However, the recommendation of a single maximum dose without regard to the site of injection is of little significance [16]. The plasma concentration of local anaesthetic drugs varies considerably as a function of the site of injection [17]. To achieve a plasma toxic concentration of lignocaine administered by subcutaneous infiltration requires a much greater dose than administration via the intercostal, extradural or brachial plexus routes [18]. Nevertheless, we did not measure serum concentrations of lignocaine in the SRA group.

The mechanism of tourniquet pain has been the subject of much debate [1, 12, 19–21]. Many factors are thought to be implicated. Cole [19] suggested that tourniquet pain had both a superficial and a deep component. Rousso and colleagues [2] and Lowrie, Jones and Eastley [12] proposed that tourniquet pain has a significant cutaneous component. In our study, EMLA and SRA provided predominantly superficial analgesia, and both provided only limited analgesia, suggesting that skin compression is one component of tourniquet pain.

The double cuff technique prevents tourniquet pain by the same mechanism as that of IVRA. The site of action of IVRA is controversial, but is explained best by multiple and complementary mechanisms [22–24]. With 0.5% lignocaine 40 ml in IVRA, the double cuff tourniquet can provide more reliable anagesia at the tourniquet site.

ACKNOWLEDGEMENT

We thank Astra Pharmaceuticals for supplying the EMLA cream.

REFERENCES

1. Farah RS, Thomas PS. Sympathetic blockade and tourniquet pain in surgery of the upper extremity. *Anesthesia and Analgesia* 1987; **66**: 1033–1035.
2. Rousso M, Wexler MR, Weinberg H, Vatashky E, Aronson B. Subcutaneous ring anesthesia in the prevention of tourniquet pain in hand surgery. *Hand* 1978; **10**: 317–320.
3. Murphy TM. Nerve blocks. In: Miller RD, ed. *Anesthesia*, 2nd Edn. New York: Churchill Livingstone, 1986; 1054–1055.
4. Rosenblatt RM, Hatherington A. Failure of transcutaneous electrical stimulation to alleviate experimental tourniquet pain. *Anesthesia and Analgesia* 1981; **60**: 720–722.
5. Gurmarnik S, Hurwitz E. Saphenous and common peroneal nerve block will prevent tourniquet pain in prolonged podiatry procedures. *Journal of Foot Surgery* 1991; **30**: 319.
6. Hopkins CS, Buckley CJ, Bush GH. Pain free injections in infants. *Anaesthesia* 1988; **43**: 198–201.
7. Hallen BH, Olsson GL, Uppfeldt A. Pain-free venepuncture. Effect of timing of application of local anaesthetic cream. *Anaesthesia* 1984; **3**: 969–972.
8. Evers H, Von Dardel O, Johlin L, Ohlsen L, Vinnars E. Dermal effects of compositions based on the eutectic mixture of lignocaine and prilocaine EMLA. Studies in volunteers. *British Journal of Anaesthesia* 1985; **57**: 997–1005.
9. Ehrenstrom Reiz GM, Reiz SL. EMLA—a eutectic mixture of local anaesthetics for topical anaesthesia. *Acta Anaesthesiological Scandinavica* 1982; **26**: 596–598.
10. Soliman IE, Broadman LM, Hannallah RS, McGill WA. Comparison of the analgesic effects of EMLA (eutectic mixture of local anesthetics) to intradermal lidocaine infiltration prior to venous cannulation in unpremedicated children. *Anesthesiology* 1988; **68**: 804–806.
11. Hallen B, Carlsson P, Uppfeldt A. Clinical study of a lignocaine–prilocaine cream to relieve the pain of venepuncture. *British Journal of Anaesthesia* 1985; **57**: 326–328.
12. Lowrie A, Jones MJ, Eastley RJ. Effect of a eutectic mixture of local anaesthetic agents (EMLA) on tourniquet pain in volunteers. *British Journal of Anaesthesia* 1989; **63**: 751–753.
13. Ogden PN. Failure of intravenous regional analgesia using a double cuff tourniquet. *Anaesthesia* 1984; **39**: 456–459.
14. Holmes CM. Intravenous regional neural blockade. In: Cousins MJ, Bridenbaugh PO, eds. *Neural Blockade in Clinical Anesthesia and Management of Pain*, 2nd Edn. Philadelphia: Lippincott, 1988; 443–459.
15. Brown EM, McGriff JT, Malinowski RW. Intravenous regional anaesthesia (Bier block): review of 20 years' experience. *Canadian Journal of Anaesthesia* 1989; **36**: 307–310.
16. Scott DB. Maximal recommended doses of local anaesthetic drugs. *British Journal of Anaesthesia* 1989; **63**: 373–374.
17. Tucker GT, Mather LE. Properties, absorption, and disposition of local anaesthetic agents. In: Cousins MJ, Bridenbaugh PO, eds. *Neural Blockade in Clinical Anesthesia and Management of Pain*, 2nd Edn.. Philadelphia: Lippincott, 1988; 62–63.
18. Scott DB, Jebson PJR, Braid DP, Ortengren B, Frisch P. Factors affecting plasma levels of lignocaine and prilocaine. *British Journal of Anaesthesia* 1972; **44**: 1040–1049.
19. Cole F. Tourniquet pain. *Anesthesia and Analgesia* 1952; **31**: 63–64.
20. Strichartz G, Zimmerman M. An explanation for pain originating from tourniquets during regional anesthesia. *Regional Anesthesia* 1984; **9**: 44–45.
21. Hagenouw RRPM, Bridenbaugh PO, Egmond JV, Stuebing R. Tourniquet pain: a volunteer study. *Anesthesia and Analgesia* 1986; **65**: 1175–1180.
22. Raj PP. Site of action of intravenous regional anesthesia. *Regional Anesthesia* 1979; **4**: 8–10.
23. Lille PE, Glynn CJ, Femwick DG. Site of action of intravenous regional anesthesia. *Anesthesiology* 1984; **61**: 507–510.
24. Rosenberg PH, Heavner JE. Multiple and complementary mechanisms produce analgesia during intravenous regional anesthesia. *Anesthesiology* 1985; **62**: 840–842.

British Journal of Anaesthesia 1993; 70: 397–401

COMPARISON OF *IN VITRO* CONTRACTURE TESTING WITH RYANODINE, HALOTHANE AND CAFFEINE IN MALIGNANT HYPERTHERMIA AND OTHER NEUROMUSCULAR DISORDERS

P. M. HOPKINS, F. R. ELLIS AND P. J. HALSALL

SUMMARY

In vitro *exposure of living skeletal muscle to ryanodine has been proposed as a potentially specific test for malignant hyperthermia (MH). In this study we have compared* in vitro *contracture responses to halothane, caffeine and ryanodine in skeletal muscle specimens obtained from 155 patients attending for diagnosis of susceptibility of MH and also from six patients having muscle biopsy for diagnosis of other neuromuscular disorders. Although the ryanodine contracture test was not specific for MH, the results suggest it may greatly aid (in conjunction with the standard halothane and caffeine contracture tests) the accurate phenotyping of individuals that is essential for the further genetic analysis of MH.* (Br. J. Anaesth. 1993; **70**: 397–401)

KEY WORDS

Hyperthermia; malignant, in vitro *test. Pharmacology: ryanodine.*

Both of the two widely used procedures for the diagnosis of malignant hyperthermia (MH) susceptibility using *in vitro* contracture tests (IVCT) with living skeletal muscle [1, 2] use separate exposure to halothane and to caffeine. The regimen of the North American MH Group also allows for a combined caffeine–halothane test [2], but recently this has been invalidated because of a high incidence of false positive results [3, 4]. The separate-exposure halothane and caffeine tests also have imperfections. Results of IVCT performed in patients with a low risk of MH ("controls") suggest a false positive rate of approximately 4 % using the European procedure [5] and 9 % using the North American procedure [3]. In our series of more than 2400 tests, 14 % of patients with an abnormal response to halothane reacted normally to caffeine, indicating the caffeine test lacks total sensitivity. Both procedures are associated also with lack of specificity, in that muscle from patients with myopathies other than MHS develop abnormal contracture responses [6, 7]. It was for these reasons, and with the need for the most accurate phenotyping of MH susceptibility for successful genetic analysis of the condition, that we investigated the potential of the plant alkaloid, ryanodine, for use in IVCT. The early results of our ryanodine contracture test were encouraging and were presented as a preliminary report [8].

We now present results from 155 patients attending for diagnosis of their MH status, on whose muscle IVCT have been done using halothane, caffeine and ryanodine. In a similar way, we also investigated muscle specimens from six patients with other neuromuscular disorders.

PATIENTS AND METHODS

Patients attending for investigation of MH status

Muscle specimens were obtained by open biopsy of the vastus medialis under regional anaesthesia (3 in 1 block) or general anaesthesia (thiopentone, fentanyl and nitrous oxide in oxygen) and maintained and used for diagnostic IVCT according to the European MH Group procedure [1]. MH status was assigned in the usual way using suitably viable specimens (twitch response > 1 g): abnormal responses to halothane (> 0.2 g contracture with $\leqslant 2\,\%$ halothane) and caffeine (> 0.2 g contracture with caffeine $\leqslant 2$ mmol litre^{-1}) indicates MH susceptible (MHS); abnormal response to only one of either halothane or caffeine indicates MH equivocal (MHE); normal responses to both drugs indicate non-susceptibility (MHN). Any muscle fascicle surplus to diagnostic requirements was used for a ryanodine contracture test (RCT). The first 63 of these were performed as described previously [8] with ryanodine added in increments at 3-min intervals to achieve muscle bath concentrations of 0.4, 0.8, 1.6 and 10 μmol litre^{-1} (RCT version 1). For the remaining 92 patients, additional ryanodine concentrations of 3.2 and 6.4 μmol litre^{-1} were included (RCT version 2). The RCT was modified in an attempt to produce a clear distinction in ryanodine threshold *concentration* between MHS and MHN groups. Initially, the threshold value of ryanodine was determined as that concentration of ryanodine at which a contracture of 0.2 g developed. This was soon changed to the concentration of ryanodine at which a sustained contracture commenced. The results presented here use this later definition for threshold value of ryanodine. For

P. M. HOPKINS, M.B., B.S., F.R.C.ANAES.; F. R. ELLIS, PH.D., F.R.C.ANAES.; P. J. HALSALL, M.B., CH.B.; Malignant Hyperthermia Investigation Unit, University Department of Clinical Medicine (Anaesthesia), St James's University Hospital, Leeds LS9 7TF.
Accepted for Publication: September 17, 1992.

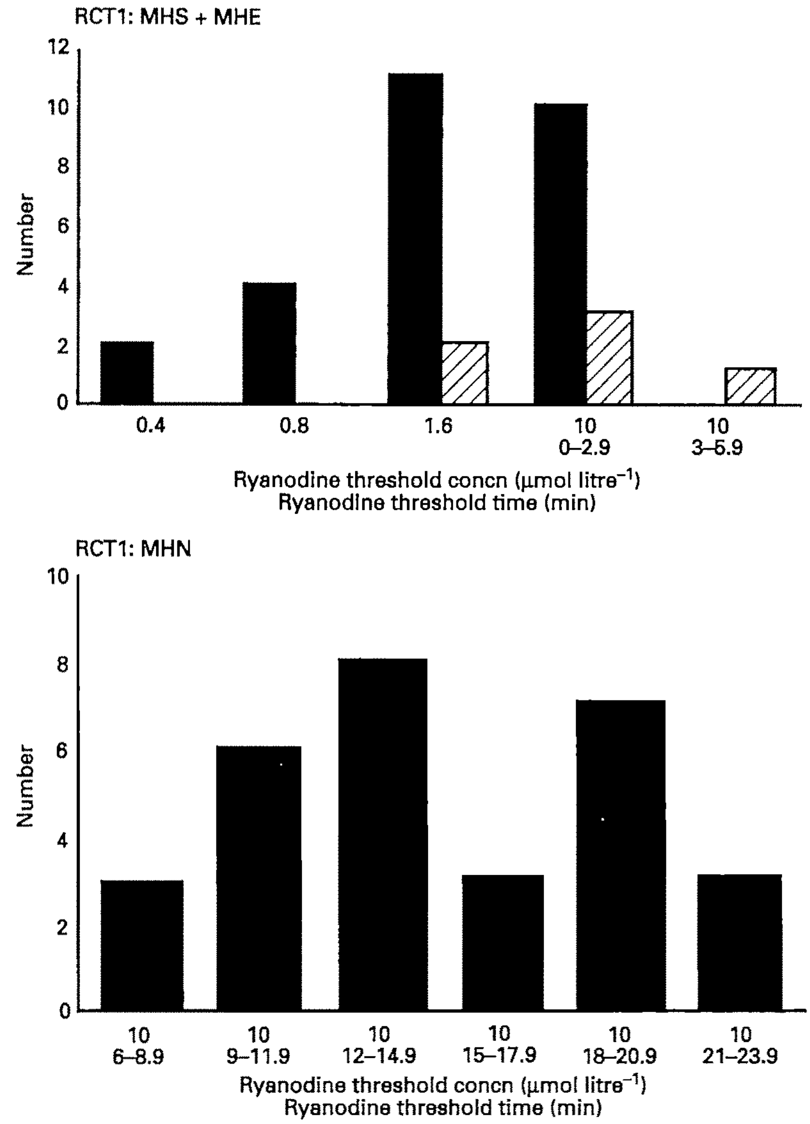


FIG. 1. Ryanodine thresholds using RCT version 1 for MHS (■) and MHE (▨) patients and for MHN patients. Ryanodine was added in increments at 3-min intervals to achieve muscle bath concentrations of 0.4, 0.8, 1.6 and 10 µmol litre^{-1}. The threshold value of ryanodine was determined as that concentration of ryanodine at which a sustained contracture commenced. If no contracture had developed within 3 min of exposure to ryanodine 10 µmol litre^{-1}, this concentration was maintained until a contracture did develop and the contracture threshold expressed as the time (in minutes) after exposure to ryanodine 10 µmol litre^{-1}.

version 1 of the RCT, where no contracture had developed within 3 min of exposure to ryanodine 10 µmol litre^{-1}, this concentration was maintained until a contracture did develop and the contracture threshold expressed as the time (in minutes) after exposure to ryanodine 10 µmol litre^{-1}.

Patients with other neuromuscular disorders

Six patients attending for muscle biopsy for histological diagnosis of a clinical neuromuscular disease were included. Surplus tissue was used for halothane, caffeine and ryanodine contracture tests that were performed as for the MH patients.

The ryanodine used (ryanodine dehydroryanodine, 98% pure) was obtained from Agri Systems Chemicals (Philadelphia, U.S.A.).

RESULTS

Patients attending for investigation of MH status

RCT version 1 (fig. 1). Of the 63 patients investigated, 27 were classified as MHS, 30 as MHN and six as MHE. All the MHS muscle fascicles developed a contracture within 3 min of exposure to the greatest concentration of ryanodine (10 µmol litre^{-1}). No MHN fascicle developed a contracture by this stage, the earliest contractures occurring after 7 min of ryanodine 10 µmol litre^{-1}. The MHE fascicles had lower thresholds than the MHN fascicles.

RCT version 2. Results of the RCT version 2 of 26 MHS, 52 MHN and 14 MHE patients are shown in figure 2. The one MHS fascicle with a ryanodine

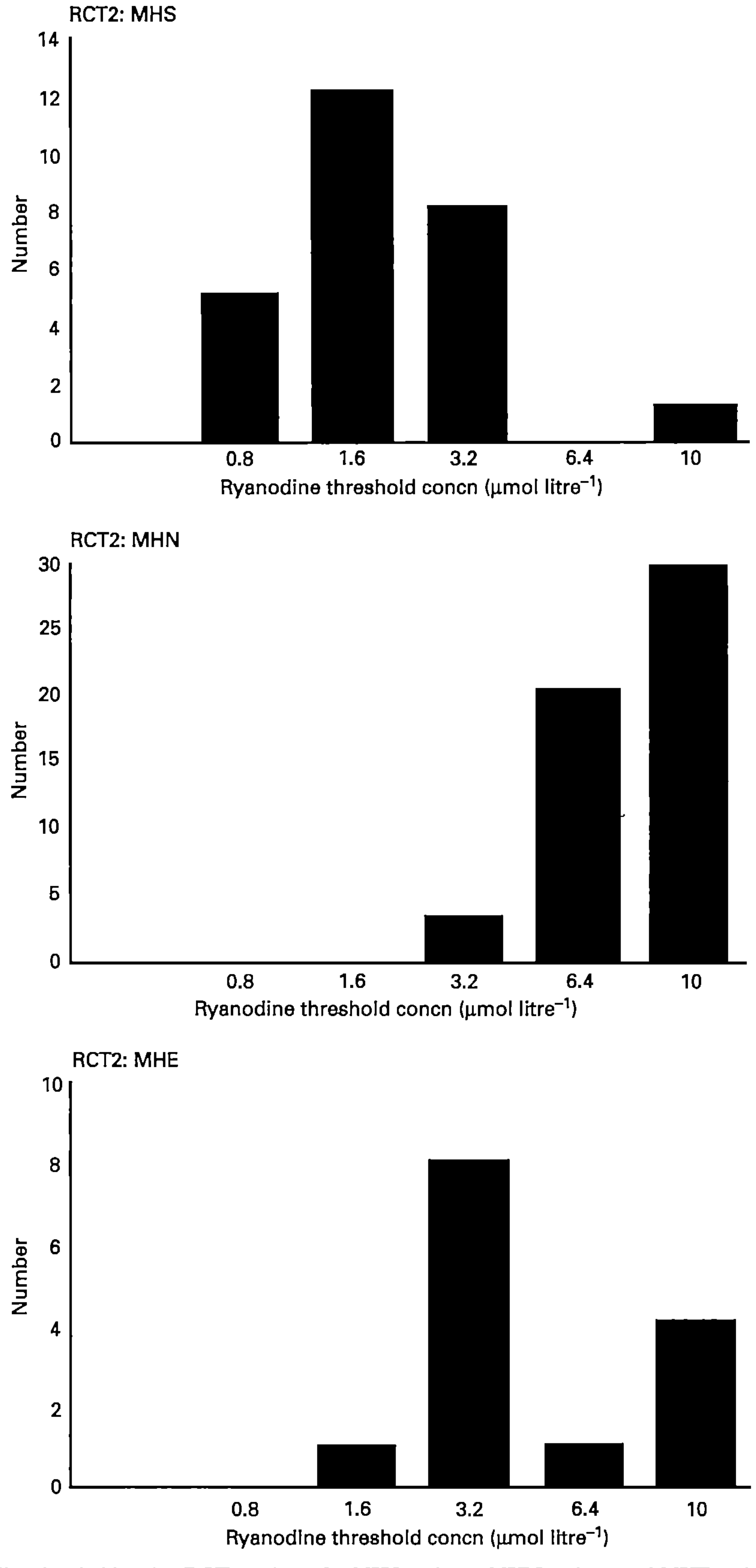


FIG. 2. Ryanodine thresholds using RCT version 2 for MHS patients, MHN patients and MHE patients. Ryanodine was added in increments at 3-min intervals to achieve muscle bath concentrations of 0.4, 0.8, 1.6, 3.2, 6.4 and 10 μmol litre^{-1}. The threshold value of ryanodine was determined as that concentration of ryanodine at which a sustained contracture commenced.

TABLE I. *Results of halothane, caffeine and ryanodine (version 2) contracture tests in individual MHE patients. Halothane test; threshold concentration of halothane and maximum force of contracture obtained at 2% halothane in the static test; DH = abnormal response to only the dynamic halothane test. For description of static and dynamic tests see [1]. * Poorly viable specimen (twitch response < 1 g), the result from which should be interpreted with caution*

	Halothane		Threshold concentration	
MHE	Threshold concn (%)	Maximum contracture (g)	Caffeine (mmol litre^{-1})	Ryanodine (μmol litre^{-1})
1	0.5	1	3	3.2
2	1	2.1	3	1.6
3	1	1.3	3	3.2
4	1	1.3	3	3.2
5	1	0.9	3	3.2
6	2	0.6	3	3.2
7	2	0.4	3	6.4
8	2	0.2	3	3.2
9	2	0.2	3	3.2
10	2	0.2	4	3.2
11	2	0.2	4	10*
12	2	0.2	> 4	10
13	1	DH	4	10
14	2	DH	> 4	10*

threshold greater than 3.2 μmol litre^{-1} was poorly viable (twitch response = 0.1 g). The halothane, caffeine and ryanodine thresholds for the important group of patients classified as MHE are shown in table I. The relationships between the thresholds in individual patients for halothane, caffeine and ryanodine (version 2) contracture tests (HCT, CCT and RCT respectively), as indicated by the Spearman rank correlation coefficient (rs) were: HCT *vs* RCT, rs = 0.737 ($P < 0.001$); CCT *vs* RCT, rs = 0.736 ($P < 0.001$); HCT *vs* CCT, rs = 0.787 ($P < 0.001$).

Patients with other neuromuscular disorders

Histological diagnosis and details of results of halothane, caffeine and ryanodine contracture tests are shown in table II. There was insufficient muscle for a caffeine contracture test in one patient.

DISCUSSION

The results of the diagnostic investigations for MH susceptibility in the 155 patients studied here are typical for our laboratory, with 34% classified as MHS, 13% MHE and 53% MHN. When the European MH Group procedure was agreed, there was a consensus that it was far more important, from a clinical perspective, to avoid false negative rather than false positive diagnoses. As one of the purposes of this process was to enable validation of results and research between European laboratories, it was necessary to set criteria for recognition of true MH positive and true MH negative patients that became, respectively, the MHS and MHN categories. It was perhaps unfortunate, and the cause of considerable confusion since, that those patients not meeting the criteria for MHS or MHN were labelled "equivocal". While this group of patients, probably, does include those with false positive results (true equivocals), the European Group's study of low risk patients indicated a false positive rate of about 4% [5]. This suggests that the majority of the MHE patients are susceptible to MH. In our laboratory, all MHE patients respond abnormally to halothane and it is our contention that this large MHE group is, therefore, a reflection of the lack of sensitivity of the caeffeine contracture test rather than a lack of specificity of the halothane contracture test. It should be noted, however, that in some centres MHE status results from an abnormal caffeine response with normal halothane response.

However, these points were only of academic importance with respect to the original goals of the European MH Group. Clinically, MHE patients usually were (and still are) regarded as susceptible to MH, but only MHS and MHN patients are entered in research programmes. Since 1984 there have been major and rapid advances in the field of molecular biology that have resulted in the real prospect of identifying the gene defect(s) responsible for MH. The nature of the required linkage studies was described elegantly by Levitt and colleagues [9], but the critical point is that their accuracy is dependent

TABLE II. *Halothane, caffeine and ryanodine contracture test results in six patients with various neuromuscular disorders. RCT version 1 was used for patients Nos 1–4; RCT version 2 used for patients Nos 5 and 6. The threshold value of ryanodine was determined as that concentration of ryanodine at which a sustained contracture commenced. If no contracture had developed within 3 min of exposure to ryanodine 10 μmol litre^{-1}, this concentration was maintained until a contracture did develop and the contracture threshold expressed as the time (in minutes) after exposure to ryanodine* 10 *μmol litre^{-1}*

		Contracture (g)			
				Ryanodine threshold	
Patient No.	Diagnosis	Halothane (force at 2%)	Caffeine (force at 2 mmol litre^{-1})	Concn (μmol litre^{-1})	Time (min)
1	Motor neurone	0.15	0	10	4
2	Facioscapulohumeral dystrophy	0.1	0.4	10	2
3	Type IIb fibre atrophy	0.2	0.1	10	5
4	Acute myositis	0.4	—	10	7
5	Acute denervation	0	0	3.2	—
6	Polymyositis	0	0	6.4	—

entirely on the accurate phenotyping of as many individuals as possible from MH families by IVCT. For these studies it is essential, therefore, that the numbers of false positive, false negative and doubtful IVCT diagnoses are minimized. To achieve this, it is clear that the MHE classification must be redressed.

Experience with the European MH Group procedure has demonstrated that positive results in two distinct tests increase the statistical confidence of the diagnosis of susceptibility to MH. This principle logically might be extended by the addition of a third test. Examination of the results obtained using RCT version 2 indicates that this warrants consideration for use as such a third test. If a ryanodine threshold of 3.2 μmol litre^{-1} or less is taken as an abnormal result, the RCT successfully identified the MHS patients (excluding the result obtained with poorly viable muscle). Furthermore, if one assumes that the MHN group are true negatives (which is highly likely), the RCT has a false positive rate of 5.8% (99% confidence interval of −2.5% to 14.1%). The most exciting aspect of the RCT, however, is that it appears to identify two populations within the MHE group, which suggests it does have the potential to distinguish positive and negative patients within this group. From this study, it is possible to conclude the following about individual MHE patients: a ryanodine threshold of 1.6 μmol litre^{-1} indicates MH susceptibility with near certainty; a ryanodine threshold of 3.2 μmol litre^{-1} indicates a probability of at least 85% of MH susceptibility; a ryanodine threshold of 10 μmol litre^{-1} indicates almost certainly non-susceptibility to MH. Although no MHS patient (with viable specimen) had a ryanodine threshold greater than 3.2 μmol litre^{-1}, an insufficient number of MHS patients has been studied to permit the conclusion that MHE patients with a ryanodine threshold of 6.4 μmol litre^{-1} are not susceptible. However, the lower limit of the 99% confidence interval for the probability that patients with a ryanodine threshold of 6.4 μmol litre^{-1} are not susceptible is 83%.

MacKenzie and colleagues [10] have suggested that the threshold force of contracture for the halothane contracture test is too low. From the results shown in table I, it can be seen that it would be unwise to increase the threshold force of contracture at 2% halothane to more than 0.2 g as, of the five patients with muscle reaching no greater force, three had a ryanodine threshold of 3.2 μmol litre^{-1}, while one had a normal response to ryanodine (threshold of 10 μmol litre^{-1}). The specimen from the fifth such patient for the RCT was poorly viable. Of course, if must be noted that the RCT may be unreliable with poorly viable specimens and we would recommend that, as stipulated in the European MH Group procedure for halothane and caeffeine tests, muscle specimens must have a twitch response of at least 1 g.

The IVCT results from muscle of patients with other neuromuscular disorders (table II) confirm earlier studies [6, 7] which demonstrated that neither halothane or caffeine contracture tests are specific for MH. The present results also show that the RCT is also not specific for MH. That the most abnormal response with the RCT was seen in denervated muscle suggests the RCT is able to detect some forms of diseased muscle (primary and secondary conditions), rather than only those caused by an abnormal ryanodine receptor protein (sarcoplasmic reticulum calcium release channel). Results of the RCT, therefore, are consistent with the hypothesis that MH is caused by an abnormal ryanodine receptor protein gene [11, 12], but equally consistent with MH being a genetically heterogeneous condition [13].

ACKNOWLEDGEMENT

We thank Mr P. L. Allam and Ms A. Clough for technical assistance.

REFERENCES

1. European Malignant Hyperpyrexia Group. A protocol for the investigation of malignant hyperpyrexia (MH) susceptibility. *British Journal of Anaesthesia* 1984; **56**: 1267–1269.
2. Larach MG, for the North American Malignant Hyperthermia Group. Standardization of the caffeine halothane muscle contracture test. *Anesthesia and Analgesia* 1989; **69**: 511–515.
3. Larach MG, Landis JR, Bunn JS, Diaz M, The North American Malignant Hyperthermia Registry. Prediction of malignant hyperthermia susceptibility in low-risk subjects. *Anesthesiology* 1992; **76**: 16–27.
4. Ellis FR, Halsall PJ, Hopkins PM. Is the "K type" halothane–caffeine responder susceptible to malignant hyperthermia? *British Journal of Anaesthesia* 1992; **69**: 468–470.
5. Ording H, for the European Malignant Hyperthermia Group. Experience with the European protocol for contracture testing. *Journal of the Neurological Sciences* 1990; **98S**: 522.
6. Lehmann-Horn F, Iaizzo PA. Are myotonias and periodic paralyses associated with susceptibility to malignant hyperthermia? *British Journal of Anaesthesia* 1990; **65**: 692–697.
7. Heiman-Patterson T, Rosenberg H, Fletcher JE, Tahmoush AJ. Halothane–caffeine contracture testing in neuromuscular diseases. *Muscle and Nerve* 1988; **11**: 453–457.
8. Hopkins PM, Ellis FR, Halsall PJ. Ryanodine contracture: a potentially specific *in vitro* diagnostic test for malignant hyperthermia. *British Journal of Anaesthesia* 1991; **66**: 611–613.
9. Levitt RC, Meyers D, Fletcher JE, Rosenberg H. Molecular genetics and malignant hyperthermia. *Anesthesiology* 1991; **75**: 1–3.
10. MacKenzie AE, Allen G, Lahey D, Crossan M, Nolan K, Mettler G, Worton RG, MacLennan DH, Korneluk R. A comparison of the caffeine halothane muscle contracture test with the molecular genetic diagnosis of malignant hyperthermia. *Anesthesiology* 1991; **75**: 4–8.
11. MacLennan DH, Duff C, Zorzato F, Fujii J, Phillips M, Korneluk RG, Frodis W, Britt BA, Worton RG. Ryanodine receptor gene is a candidate for predisposition to malignant hyperthermia. *Nature (London)* 1990; **343**: 559–561.
12. Healy JMS, Heffron JJA, Lehane M, Bradley DG, Johnson K, McCarthy TV. Diagnosis of susceptibility to malignant hyperthermia with flanking DNA markers. *British Medical Journal* 1991; **303**: 1225–1228.
13. Ball SP, Dorkins H, Ellis FR, Hall JL, Halsall PJ, Hopkins PM, Stewart AD. Is muscle biopsy for malignant hyperthermia diagnosis still necessary? *British Journal of Anaesthesia* 1992; **69**: 222P–223P.

British Journal of Anaesthesia 1993; **70**: 402–404

RECOVERIES OF POST-TETANIC TWITCH AND TRAIN-OF-FOUR RESPONSES AFTER ADMINISTRATION OF VECURONIUM WITH DIFFERENT INHALATION ANAESTHETICS AND NEUROLEPTANAESTHESIA

Y. SAITOH, H. TOYOOKA AND K. AMAHA

SUMMARY

We have studied recovery of post-tetanic twitch (PTT) and train-of-four (TOF) responses after administration of vecuronium in 100 patients under different inhalation anaesthetics and neuroleptanaesthesia. Patients were allocated randomly to five groups of 20 patients each to receive: neuroleptanaesthesia (droperidol and fentanyl), halothane, isoflurane, enflurane or sevoflurane (1 MAC in nitrous oxide and oxygen). The times from initial administration of vecuronium 0.2 mg kg^{-1} to the first appearances of T1, T2, T3 and T4 differed significantly between groups. However, the intervals to the first appearance of PTT$_1$, PTT$_{10}$ and PTT$_{20}$ did not differ significantly between groups. (Br. J. Anaesth. 1993; **70**: 402–404)

KEY WORDS

Monitoring: post-tetanic-twitch, train-of-four. Neuromuscular relaxants: vecuronium.

Post-tetanic twitch (PTT) is a valuable method for evaluating intense neuromuscular block, because PTT response can be observed earlier than train-of-four (TOF) response during recovery of neuromuscular transmission after non-depolarizing neuromuscular blocking agents [1–3]. Recovery of TOF or single twitch responses under different types of anaesthesia has been studied by several authors [4–8], but recovery of PTT responses has not been reported. We have studied the intervals between initial administration of vecuronium to the first appearances of PTT$_1$, PTT$_{10}$, PTT$_{20}$, T1, T2, T3 and T4 with different inhalation anaesthetics and neuroleptanaesthesia, and evaluated the use of PTT in assessing the degree of neuromuscular block.

PATIENTS AND METHODS

With institutional Review Board approval and written informed consent, we studied 100 adult patients (53 male), ASA class I or II, undergoing elective general surgical, orthopaedic, gynaecological, urological, ENT or ophthalmological procedures. None of the patients had neuromuscular, renal or hepatic disorders or received any medication that might alter neuromuscular transmission. They were allocated randomly to five groups of 20 patients each to receive: neuroleptanaesthesia (NLA group), halothane (group H), isoflurane (group I), enflurane (group E) or sevoflurane (group S). All the patients were premedicated with atropine 0.01 mg kg^{-1} and hydroxyzine 1 mg kg^{-1} i.m. 1 h before operation. Stimulating surface electrodes were placed on the ulnar nerve at the elbow and recording electrodes on the corresponding abductor digiti minimi muscle. After induction of anaesthesia with sodium thiamylal 5 mg kg^{-1}, the ulnar nerve was stimulated supramaximally (50 mA) with an electrical stimulator (SEN-3201, Nihon-Kohden Inc., Tokyo). Rectangular pulses of 0.1 ms duration were triggered automatically by a computer to produce two patterns of electrical stimulation (TOF and PTT) as described below. When the response to TOF stimulation was stable, the magnitude of the first twitch of the train was taken as the control twitch height. Vecuronium 0.2 mg kg^{-1} i.v. was then administered to facilitate tracheal intubation. Anaesthesia was maintained with 66 % nitrous oxide in oxygen and fentanyl 5 μg kg^{-1} and droperidol 0.2 mg kg^{-1} in the NLA group. In the other groups, anaesthesia was maintained with 66 % nitrous oxide in oxygen and 1 MAC end-tidal inhalation anaesthetic (0.76 % halothane, 1.15 % isoflurane, 1.68 % enflurane or 1.71 % sevoflurane). The end-tidal concentrations of carbon dioxide, nitrous oxide, and inhalation anaesthetics were measured by infra-red absorption using a Capnomac Ultima-S-31-03 (Datex Inc., Helsinki) calibrated with standard gases. Patient's lungs were ventilated to normocapnia as measured by end-tidal carbon dioxide and intermittent arterial blood-gas analysis. Rectal temperature was maintained at 35.5–36.8 °C with warming blankets. During the first 5 min after a control measurement was obtained, TOF stimuli were applied every 5 s to monitor relaxation for tracheal intubation. Five minutes after a control measurement was obtained, the intervals between TOF stimuli were changed to

---

YUHJI SAITOH, M.D.; HIDENORI TOYOOKA, M.D.; KEISUKE AMAHA, M.D.; Department of Anaesthesiology and Critical Care Medicine, Faculty of Medicine, Tokyo Medical and Dental University, 5–45, Yushima, 1-Chome, Bunkyo-ku, Tokyo 113, Japan. Accepted for Publication: September 17, 1992.

TABLE I. *Characteristics of the patients studied (mean (range or* SD*)). No significant differences in number of patients, age, sex, height and body weight between groups (n = 20 each group). NLA = Neuroleptanaesthesia; H = halothane; I = isoflurane; E = enflurane; S = sevoflurane*

	NLA	H	I	E	S
Age (yr)	51.8 (23–78)	48.5 (20–81)	51.3 (22–72)	49.5 (20–77)	49.7 (23–77)
Sex (M/F)	10/10	10/10	11/9	11/9	11/9
Height (cm)	162.2 (12.4)	162.3 (13.0)	159.6 (12.1)	159.9 (13.4)	162.4 (13.1)
Body weight (kg)	56.4 (6.2)	55.4 (7.0)	56.1 (7.9)	57.7 (7.4)	57.5 (7.7)

TABLE II. *Intervals from initial administration of vecuronium to the first appearances of PTT_1, PTT_{10} and PTT_{20} in the five groups (mean (*SD*)). No significant differences between groups. NLA = Neuroleptanaesthesia; H = halothane; I = isoflurane; E = enflurane; S = sevoflurane*

	NLA	H	I	E	S
Time of appearance (min)					
PTT_1	32.05 (6.53)	30.69 (7.35)	31.62 (5.39)	31.20 (4.27)	31.93 (5.72)
PTT_{10}	43.05 (8.81)	43.39 (9.10)	45.09 (11.00)	42.84 (8.85)	47.71 (12.42)
PTT_{20}	50.94 (9.15)	50.98 (9.77)	54.80 (10.72)	52.18 (10.15)	56.72 (13.36)

TABLE III. *Intervals from initial administration of vecuronium to the first appearances of T1, T2, T3 and T4 in the five groups (mean (*SD*)). ** Significantly different from NLA and H groups (P < 0.01). NLA = Neuroleptanaesthesia; H = halothane; I = isoflurane; E = enflurane; S = sevoflurane*

	NLA	H	I	E	S
Time of appearance (min)					
T1	39.89 (8.53)	40.12 (8.90)	45.22 (7.64)	46.11 (5.86)**	47.18 (9.69)**
T2	50.02 (10.77)	49.49 (7.22)	55.52 (9.03)	58.45 (10.06)**	59.42 (10.13)**
T3	55.26 (12.04)	55.83 (10.05)	62.15 (8.74)	66.18 (13.05)**	67.67 (10.93)**
T4	58.18 (12.07)	58.31 (10.12)	64.80 (9.20)	69.60 (13.64)**	70.91 (10.88)**

30 s and PTT stimuli were substituted for TOF stimuli every 150 s. This pattern of stimulation was continued until the end of anaesthesia; thereafter, 100 % oxygen was given to the patients and atropine 1 mg and neostigmine 2 mg i.v. were given to antagonize any residual neuromuscular block.

For TOF stimulation, a series of four pulses was applied at 2 Hz for 2 s. For PTT, a tetanic stimulus (50 Hz) was applied for 5 s and, after an interval of 3 s, single twitch stimuli (1 Hz) were applied for 20 s. The EMG response of each stimulus was amplified via an isolated differential amplifier (AVB-11, Nihon-Kohden Inc., Tokyo) and displayed on an oscilloscope (VC-11, Nihon-Kohden Inc., Tokyo). These EMG signals were then gated (gate open from 3 to 25 ms after test stimuli) to reduce the stimulation artefact, rectified and integrated for each single response, using a specially designed integrator with reset and sample hold circuit, by digital commands from a computer. Integrated data sets of either TOF or PTT responses were displayed on a monitoring oscilloscope and stored on hard disc. A personal desk-top computer (PC-9801 UX, NEC Inc., Tokyo) was used for overall control of automatic stimulation–data collection sequences, and for later data analysis. The intervals from initial administration of vecuronium to first appearance of PTT_1, PTT_{10}, PTT_{20}, T1, T2, T3 and T4 were calculated. The responses to electrical stimuli were considered to be detectable when the magnitudes were larger or equal to 1 % of control.

Statistical analysis was performed using ANOVA and Duncan's multiple range test [9] to test for differences between the five groups, $P < 0.01$ being considered significant. All results are expressed as mean (SD).

RESULTS

There were no significant differences in patient characteristics between the five groups (table I).

The interval to the first appearances of PTT_1, PTT_{10} and PTT_{20} did not differ significantly between the five groups (table II).

The intervals to the first appearances of T1, T2, T3 and T4 in groups E and S differed significantly from those in the NLA group and group H. However, those in group I were not significantly different from those in the four other groups (table III).

DISCUSSION

Recovery of post-tetanic twitch is a valuable indicator for evaluating intense neuromuscular block produced by non-depolarizing neuromuscular blocking agents, because the appearance of PTT responses can be observed earlier than TOF responses during the recovery of neuromuscular transmission [1–3].

Baker and colleagues [10] and Riker [11] reported that PTT was a sensitive index of neuromuscular block produced by non-depolarizing neuromuscular blocking agents at the prejunctional region (motor nerve endings); however, twitch heights of TOF in comparison with control twitch height are affected by postjunctional effects [12, 13]. It is known also that inhalation anaesthetics act mainly in the postjunctional region of the neuromuscular junction and prolong the duration of neuromuscular block produced by non-depolarizing neuromuscular blocking agents to varying degrees [4, 5, 12, 14, 15]. Kennedy and Galindo [14] reported that enflurane reinforced the muscle twitch depression produced by tubocurarine in the rat phrenic nerve–diaphragm preparation and that it was caused primarily by the postjunctional effect. Gissen, Karis and Nastuk [15] showed, in the frog sciatic nerve–sartorius muscle, that the structure most sensitive to the neuromuscular blocking action of halothane is the postjunctional membrane. Thus the inhalation anaesthetics prolong the duration of neuromuscular block produced by non-depolarizing neuromuscular blocking agents, by acting mainly at the postjunctional membrane. Therefore it is not surprising that the appearance of PTT, an index of prejunctional block, did not differ between our five groups, whereas the appearance of T1–T4, an index of postjunctional block, differed significantly between the groups. We found that, in ranking order, sevoflurane, enflurane, isoflurane and halothane prolonged the intervals to the first appearance of T1–T4. This is in agreement with previous studies [4–8].

There was little difference in the first appearances of T1–T4 between the NLA group and group H. Bonsu and colleagues [1] found that the interval from the first appearance of PTT_1 to that of T1 was 9 min with halothane anaesthesia, and 10 min with fentanyl anaesthesia after administration of atracurium 0.6 mg kg^{-1}; the difference was not significant.

Itagaki and colleagues [4], Miller and colleagues [16] and Vitez and colleagues [17] reported that halothane increased blood flow in skeletal muscle to a smaller extent than that caused by other inhalation anaesthetics. This may explain partly why halothane apparently did not prolong the duration of neuromuscular block. As isoflurane takes 90 min [18] and enflurane takes 200–240 min [19] to reach the neuromuscular junction in effective concentrations, and because the end-tidal concentration of inhalation anaesthetics may not equilibrate with inspired concentrations until at least 20 min after commencement of administration [20, 21], we may have underestimated the prolongation of vecuronium-induced neuromuscular block by the inhalation anaesthetics.

It is possible that relatively short interval (2.5 min) between stimuli with PTT may have influenced recovery of neuromuscular transmission in the arm investigated [22]. We used this interval because of the relatively rapid recovery from neuromuscular block produced by vecuronium, but this problem may require further investigation. Moreover, the interval between stimuli with TOF during the induction of anaesthesia (5 s) may have been too short. This pattern of stimulation was used in order to determine the appropriate moment for smooth tracheal intubation. However, the interval was changed subsequently to 30 s and this duration would have little influence, if any, on subsequent evaluation of the neuromuscular block [23].

REFERENCES

1. Bonsu AK, Mogensen JV, Fernando PUE, Muchhal K, Tamilarasan A, Lambourne A. Relationship of post-tetanic count and train-of-four response during intense neuromuscular blockade caused by atracurium. *British Journal of Anaesthesia* 1987; **59**: 1089–1092.
2. Ridley SA, Hatch DJ. Post-tetanic count and profound neuromuscular blockade with atracurium infusion in paediatric patients. *British Journal of Anaesthesia* 1988; **60**: 31–35.
3. Mogensen JV, Hansen PH, Jorgensen BC, Ording H, Engbæk J, Nielsen A. Post-tetanic count (PTC): A new method of evaluating an intense nondepolarizing neuromuscular blockade. *Anesthesiology* 1981; **55**: 458–461.
4. Itagaki T, Tai K, Katsumata N, Suzuki F. A clinical and experimental study on potentiation with sevoflurane of neuromuscular blocking effects of vecuronium bromide. *Masui (Japanese Journal of Anesthesiology)* 1988; **37**: 943–948.
5. Tai K, Suzuki H, Itagaki T, Katsumata N, Nakamura T, Yamada M, Shiraishi H. Influence of sevoflurane on neuromuscular blocking effects of vecuronium and pancuronium. *Masui (Japanese Journal of Anesthesiology)* 1987; **36**: 227–232.
6. Rupp SM, Miller RD, Gencarelli PJ. Vecuronium-induced neuromuscular blockade during enflurane, isoflurane, and halothane anesthesia in humans. *Anesthesiology* 1984; **60**: 102–105.
7. Ali HH, Savarese JJ. Monitoring of neuromuscular function —symposium on monitoring. *Anesthesiology* 1976; **45**: 216–249.
8. Foldes FF, Benici A, Newton D. Influence of halothane and enflurane of the neuromuscular effects of Org NC 45 in man. *British Journal of Anaesthesia* 1980; **52** (Suppl. 1): 64S.
9. Miller JG. *Simultaneous Statistical Inference*. New York: McGraw-Hill, 1966.
10. Baker T, Aguero A, Stanec A, Lowndes HE. Prejunctional effects of vecuronium in the cat. *Anesthesiology* 1986; **65**: 480–484.
11. Riker WF Jr. Prejunctional effects of neuromuscular blocking and facilitatory drugs. In: Katz RL, ed. *Muscle Relaxants*. New York: North-Holland Publishing, 1975: 59–102.
12. Stanec A, Baker T. Prejunctional and postjunctional effects of tubocurarine and pancuronium in man. *British Journal of Anaesthesia* 1984; **56**: 607–611.
13. Pearce AC, Casson WR, Jones RM. Factors affecting train-of-four fade. *British Journal of Anaesthesia* 1985; **57**: 602–606.
14. Kennedy R, Galindo A. Neuromuscular transmission in a mammalian preparation during exposure to enflurane. *Anesthesiology* 1975; **42**: 432–442.
15. Gissen AJ, Karis JH, Nastuk WL. Effect of halothane on neuromuscular transmission. *Journal of the American Medical Association* 1966; **197**: 116–120.
16. Miller RD, Way WL, Dolan WM, Stevens WC, Eger EI II. Comparative neuromuscular effects of pancuronium, gallamine, and succinylcholine during forane and halothane anesthesia in man. *Anesthesiology* 1971; **35**: 509–514.
17. Vitez TS, Miller RD, Eger EI II, Nyhuis LSV, Way WL. Comparison *in vitro* of isoflurane and halothane potentiation of d-tubocurarine and succinylcholine neuromuscular blockades. *Anesthesiology* 1974; **41**: 53–56.
18. Eriksson LI, Staun P, Lennmarken C. The influence of 0.5% isoflurane on a vecuronium-induced neuromuscular blockade. *Acta Anaesthesiologica Scandinavica* 1989; **33**: 309–312.
19. Eger EI II. *Anesthetic Uptake and Action*. Baltimore: Williams and Wilkins, 1974; 82.
20. Steffey EP, Johnson BH, Eger EI II, Howland D. Nitrous oxide: Effect on accumulation rate and uptake of bowel gases. *Anesthesia and Analgesia* 1979; **58**: 405–408.
21. Torri G, Damia G, Fabiani ML. Effect of nitrous oxide on the anaesthetic requirement of enflurane. *British Journal of Anaesthesia* 1974; **46**: 468–472.
22. Feldman SA, Tyrell MF. A new theory of the termination of action of the muscle relaxants. *Proceedings of The Royal Society of Medicine* 1970; **63**: 692–695.
23. Mogensen JV. Clinical assessment of neuromuscular transmission. *British Journal of Anaesthesia* 1982; **54**: 209.

British Journal of Anaesthesia 1993; 70: 405–410

PREJUNCTIONAL ACTION OF NEOSTIGMINE ON MOUSE NEUROMUSCULAR PREPARATIONS

M. F. M. BRAGA, E. G. ROWAN, A. L. HARVEY AND W. C. BOWMAN

SUMMARY

We have studied the effects of neostigmine on the mouse diaphragm and triangularis sterni isolated nerve–muscle preparations. Mechanical responses of the muscle, end-plate potentials and miniature end-plate potentials, and extracellularly recorded nerve ending currents were recorded. In the mouse diaphragm nerve–muscle preparations, neostigmine 1 µmol litre^{-1} *continued to produce some antagonism of tubocurarine-induced block after cholinesterase had been inactivated completely by di-isopropyl fluorophosphate 22 µmol litre*$^{-1}$*. In the mouse triangularis sterni preparation, neostigmine 0.1–1 µmol litre*$^{-1}$ *increased the quantal content of the end-plate potential in a concentration-dependent manner. This effect appeared to be sufficient to account for the cholinesterase-independent antagonistic action to tubocurarine under the conditions of the experiments. Neostigmine 1–100 µmol litre*$^{-1}$ *depressed the amplitude of the* K^+ *currents of the perineural waveforms in a concentration-dependent manner, and this may account for its ability to increase the quantal content of the end-plate potential. Although inhibition of acetylcholinesterase is the main mechanism of action of neostigmine, the drug also exerts an additional direct action on motor nerve endings to block the delayed rectifier* K^+ *channels and enhance transmitter release. This effect occurred at clinically relevant concentrations of neostigmine. Physostigmine and pyridostigmine did not possess this additional action.* (Br. J. Anaesth. 1993; **70**: 405–410)

KEY WORDS

Antagonists: neostigmine. Neuromuscular function: acetylcholine release.

Neostigmine is an anticholinesterase agent used to antagonize neuromuscular block produced by non-depolarizing blocking drugs. While neostigmine undoubtedly inhibits the acetylcholinesterase of the neuromuscular junction, it is not certain if this is the only mechanism whereby it facilitates transmission at this site [for reviews of the literature see 1–3]. It has been suggested that, in addition to inhibiting cholinesterases, the drug acts directly on post-junctional acetylcholine receptors [4–7] or acts on the nerve endings to increase the quantal content of the end-plate potential [8], possibly by increasing the number of functional release sites [9]. In large concentrations, the drug may impair neuromuscular transmission by occluding the acetylcholine receptor-operated ion channels [10].

In the experiments described in this paper, we have studied the effects of neostigmine on the mouse diaphragm and triangularis sterni isolated nerve–muscle preparations in an attempt to elucidate the complex actions of this drug at the neuromuscular junction. In particular, we have studied the effects of small concentrations of neostigmine which should be clinically relevant. We have measured mechanical responses of diaphragm preparations to direct electrical stimulation and to nerve stimulation in order to distinguish between possible effects on neuromuscular transmission and on muscle contractility. Intracellular recordings were made from muscle end-plate regions; by comparing effects on end-plate potentials (EPP) evoked by nerve stimulation and on spontaneously occurring miniature end-plate potentials (MEPP), actions on the quantal release of acetylcholine can be determined. Extracellularly recorded nerve ending currents (perineural waveforms) have been recorded in order to reveal possible effects of neostigmine on ion channels in motor nerves.

MATERIALS AND METHODS

Mouse diaphragm nerve–muscle preparations

We dissected phrenic nerve–hemidiaphragm preparations from 15–25 g male mice (Balb C strain) killed by exsanguination after cervical dislocation. The preparations were mounted in 10-ml tissue baths containing physiological salt solution of the following composition (mmol litre^{-1}): NaCl, 118.4; KCl, 4.7; $MgSO_4$, 1.2; KH_2PO_4, 1.2; $CaCl_2$, 2.5; $NaHCO_3$, 25; glucose, 11.1. The solution was maintained at pH 7.3 and bubbled with oxygen containing 5% carbon dioxide. Experiments were carried out at room temperature (20–25 °C). The phrenic nerve was stimulated at frequencies of 0.1 or

---

M. F. M. BRAGA, L.D.S., M.SC.; E. G. ROWAN, B.SC., PH.D.; A. L. HARVEY, B.SC., PH.D.; W. C. BOWMAN, PH.D., D.SC., F.R.S.E., HON. F.R.C.ANAES.; Department of Physiology and Pharmacology, and Strathclyde Institute for Drug Research, University of Strathclyde, Glasgow G1 1XW. Accepted for Publication: October 6, 1992.

Correspondence to W.C.B.

0.05 Hz with rectangular pulses of 0.2 ms duration and of a strength greater than that required to produce maximal twitches. In addition, the muscle was stimulated directly at a frequency of 0.05 Hz with rectangular pulses of 2 ms duration and strength greater than that required to produce maximal twitches. Twitches were recorded isometrically on Grass 79B and Washington ink writing polygraphs using Grass FT03 or SRI force transducers.

We studied the effects of neostigmine on neurally evoked twitches after a 70% reduction in twitch amplitude had been produced by tubocurarine 0.2–2.0 μmol $litre^{-1}$ or by physiological salt solution containing low Ca^{2+} (0.5 mmol $litre^{-1}$) and high Mg^{2+} (2.5–5.0 mmol $litre^{-1}$). The latter conditions were used to reduce acetylcholine release in an attempt to reveal possible presynaptic actions of neostigmine. In some experiments, neostigmine was tested during partial block produced by α-bungarotoxin and also on directly evoked twitches after neuromuscular transmission had been abolished by α-bungarotoxin. In these experiments, the concentrations of neostigmine were increased cumulatively when the twitch height had stabilized after the previous addition. In other experiments, partial paralysis was induced by tubocurarine and antagonized by the organophosphate anticholinesterase di-isopropyl fluorophosphate (DFP). Additional tubocurarine was given to re-establish a partial block, and antagonism was attempted with DFP, neostigmine, physostigmine or pyridostigmine.

Mouse triangularis sterni preparations

Experiments were performed at room temperature (20–25 °C). The left triangularis sterni nerve–muscle preparation [11] was isolated from 15–25 g male mice (Balb C strain). During dissection, the muscle with its three nerves was perfused continuously with the physiological salt solution described above. The preparation was pinned thoracic side downwards to the base of a 3-ml tissue bath and perfused at a rate of 5–10 ml min^{-1} with the physiological salt solution described above, to which tubocurarine 10 μmol $litre^{-1}$ (for extracellular recording) or Mg^{2+} 2–5 mmol $litre^{-1}$ (for intracellular recording) was added to prevent muscle twitching. In all Mg^{2+}-paralysed preparations, the Ca^{2+} concentration was reduced to 0.5 mmol $litre^{-1}$ and 20 min allowed for equilibration. The intercostal nerves were stimulated via a suction electrode every 2 s with pulses of 50 μs duration and supramaximal strength.

Intracellular recording. Neuromuscular junctions were identified by the presence of EPP and MEPP with rise times of 1 ms or less. EPP and MEPP were recorded using glass microelectrodes filled with potassium chloride 3 mol $litre^{-1}$ (resistance 5–20 MΩ), as described previously [12]. Neostigmine was added cumulatively (from 0.1 to 10 μmol $litre^{-1}$) and the concentration of neostigmine was increased when its effect on EPP amplitude and time course had stabilized after previous addition of the drugs. Recordings were made continuously from one end-plate area before and throughout application of drugs. The potentials were recorded, amplified and stored as described previously [12]. The time constants of decay of EPP and MEPP were measured in order to quantify the prolongation of action of acetylcholine in the presence of an anticholinesterase. Quantal content (the average number of packets of acetylcholine released in response to nerve stimulation) was determined by dividing the mean amplitude of EPP by the mean amplitude of MEPP recorded from the same site.

Extracellular recording. Presynaptic waveforms generated by nerve action potentials were recorded by a glass microelectrode (filled with sodium chloride 2 mol $litre^{-1}$, resistance 5–15 MΩ) placed inside the perineural sheath (near end-plate areas) of one of the branches of an intercostal nerve [13–15]. The potentials were recorded, amplified and stored as for the intracellular recordings. Usually, 20 to 25 waveforms were recorded at each time period. As the shape of the waveform recorded is dependent on the electrode position, waveforms were monitored continuously from the same site before and throughout application of drugs. Recording sites were rejected if the signal amplitude decreased by more than 10% during the first 20 min before the addition of the compounds. Using this design, stable recordings could be obtained over a 180-min period in control solutions or in the presence of drugs.

Materials

All the compounds were obtained from Sigma Chemical Co., Poole, Dorset.

Analysis and statistics

The recording system had an overall passband of d.c.-10 kHz and signals were digitized at 25 kHz, which was more than twice the filter cut off frequency (Nyquist criteria). The signals were analysed with a suite of purpose-designed programs [16] running on an IBM-compatible microcomputer (Vanilla, 286-12A).

Values in the text are mean (SE) of at least four experiments, unless stated otherwise. Differences between means were tested using the Mann–Whitney *U* test, $P < 0.05$ being taken as significant.

RESULTS

Mouse diaphragm nerve–muscle preparations

Neostigmine antagonized a 70% reduction of indirectly elicited twitch height induced by tubocurarine 0.2–2 μmol $litre^{-1}$. Complete antagonism of tubocurarine paralysis was produced with neostigmine 0.1 μmol $litre^{-1}$, and in the presence of greater concentrations (1–10 μmol $litre^{-1}$), augmentation of the maximal twitches from control was induced, presumably because the action of acetylcholine was prolonged sufficiently to induce repetitive muscle action potentials and consequent tetanic contractions (fig. 1). However, neostigmine only partially antagonized the 70% reduction in indirectly elicited twitch height induced by physiological salt solution containing Ca^{2+} 0.5 mmol $litre^{-1}$ and Mg^{2+} 2.5–5 mmol $litre^{-1}$. The threshold concentration was 0.1 μmol $litre^{-1}$ and the maximum recovery was about 72% (fig. 1). In contrast, neostigmine

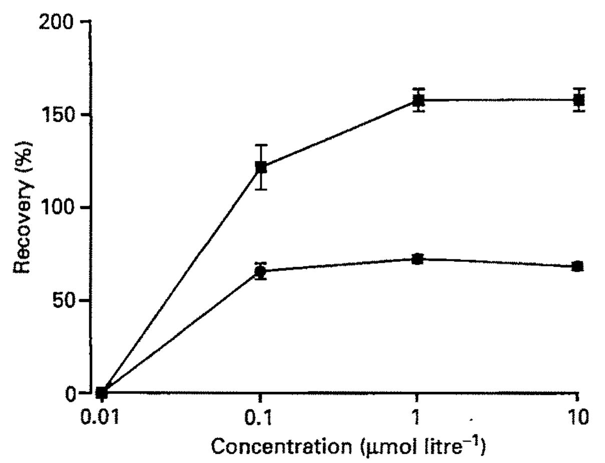


FIG. 1. Antagonism of tubocurarine block by neostigmine (■), and antagonism of low Ca^{2+}–high Mg^{2+} block by neostigmine (●): responses of mouse hemidiaphragm nerve–muscle preparations to indirect muscle stimulation once every 10 s. Experiments were carried out at room temperature (20–25 °C). Points are means of four experiments, and SE are indicated by the bars unless smaller than symbols.

1–10 μmol $litre^{-1}$ failed to antagonize the block induced by α-bungarotoxin 500 nmol $litre^{-1}$ (an irreversible blocker of nicotinic cholinoceptors) or to increase directly elicited twitch height when neuromuscular transmission was blocked completely by α-bungarotoxin 500 nmol $litre^{-1}$ (fig. 2).

In order to investigate if neostigmine has any facilitatory effects on neuromuscular transmission independent of its anticholinesterase activity, experiments were carried out in which a 70 % block of indirectly elicited twitch height induced by tubocurarine 0.2–2 μmol $litre^{-1}$ was antagonized completely by DFP 22 μmol $litre^{-1}$. (DFP is an irreversibly acting organophosphate anticholinesterase agent.) Then, a subsequent addition of tubocurarine 0.3–1 μmol $litre^{-1}$ was used in order to induce a 70 % block of indirectly elicited twitch height. Under these conditions, addition of DFP 11 μmol $litre^{-1}$ failed to increase twitch height. However, addition of neostigmine 1 μmol $litre^{-1}$ produced a further increase in twitch height of 37 (4) % ($n = 4$) (fig. 3). Physostigmine 0.1–10 μmol $litre^{-1}$ and pyridostigmine 0.1–10 μmol $litre^{-1}$, when tested under the same conditions, did not produce further increase in twitch height; for example with 3 μmol $litre^{-1}$, twitch height with physostigmine and pyridostigmine remained at 102 (7) % ($n = 4$) and 96 (8) % ($n = 4$), respectively, of the partially blocked values. The greatest concentrations of both compounds (10 μmol $litre^{-1}$) caused a reduction in twitch height (data not shown).

Mouse triangularis sterni nerve–muscle preparations

Intracellular recording. In Mg^{2+}-paralysed preparations, control MEPP were 0.32–0.71 mV in amplitude and had a time constant of decay of 1.5–2.1 ms. The EPP were 1.1–3.5 mV in amplitude and had a time constant of decay of 1.3–2.2 ms at a resting membrane potential of −65 to −85 mV. Neostigmine 0.1–1 μmol $litre^{-1}$ increased quantal content (fig. 4A). For example, quantal content was increased by 20 (6) % ($n = 3$) and by 79 (28) % ($n = 4$) by neostigmine 0.1 and 1.0 mmol $litre^{-1}$, respectively (fig. 4A). However, in the presence of greater concentrations of neostigmine (3–10 μmol $litre^{-1}$), the quantal content was reduced towards control values (fig. 4A). As would be expected with an anticholinesterase, neostigmine 0.1–1 μmol $litre^{-1}$ also increased the time constant of decay of the MEPP and EPP in a concentration-dependent manner, until the time course was about 200 % of control (fig. 4A, B). With greater concentrations of neostigmine (3–10 μmol $litre^{-1}$), the increase in the time constant of decay was less pronounced (fig. 4A, B). In addition, neostigmine 0.1–1 μmol $litre^{-1}$ increased EPP and MEPP amplitude (fig. 4A, B). However, greater concentrations of neostigmine (3–10 μmol $litre^{-1}$) reduced the amplitude of MEPP and of EPP to values less than control (fig. 4A, B).

Extracellular recording. The perineural waveform is composed predominantly of two negative deflections, usually preceded by a small positivity as the action potential arrives near the nerve endings.

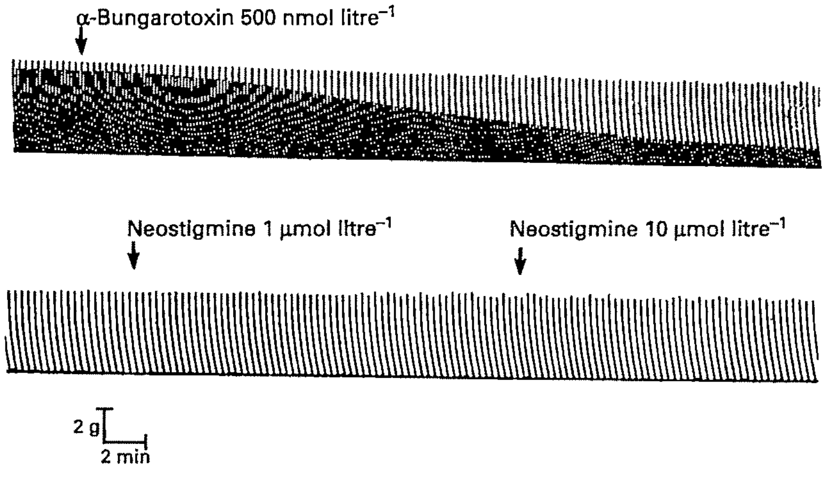


FIG. 2. Indirectly elicited (smaller traces) and directly elicited (larger traces) twitches of an isolated phrenic nerve–hemidiaphragm preparation. Indirectly elicited twitches were blocked by α-bungarotoxin 500 nmol $litre^{-1}$. Neostigmine 1–10 μmol $litre^{-1}$ failed to increase the directly elicited twitch height or to antagonize the α-bungarotoxin-induced neuromuscular paralysis. Experiments were carried out at room temperature (20–25 °C). Preparations were stimulated once every 10 s.

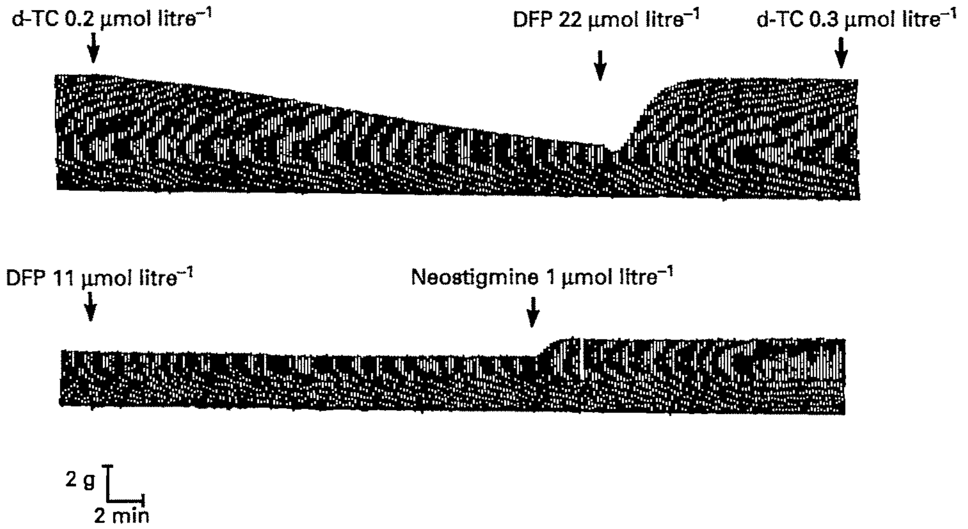


FIG. 3. Isolated phrenic nerve–hemidiaphgram preparation. Antagonism by DFP 22 μmol litre^{-1} of a 70% block of indirectly elicited twitch height induced by tubocurarine (d-TC) 0.2 μmol litre^{-1}. Then, a subsequent addition of tubocurarine 0.3 μmol litre^{-1} was used in order to induce, again, a 70% block of indirectly elicited twitch height. Under these conditions, a subsequent addition of DFP 11 μmol litre^{-1} failed to increase twitch height but the addition of neostigmine 1 μmol litre^{-1} could induce a further increase in twitch height. Experiments were carried out at room temperature (20–25 °C). Preparations were stimulated once every 10 s. Note that there is a 23-min gap in the recordings shown in the figure between the upper and lower panels.

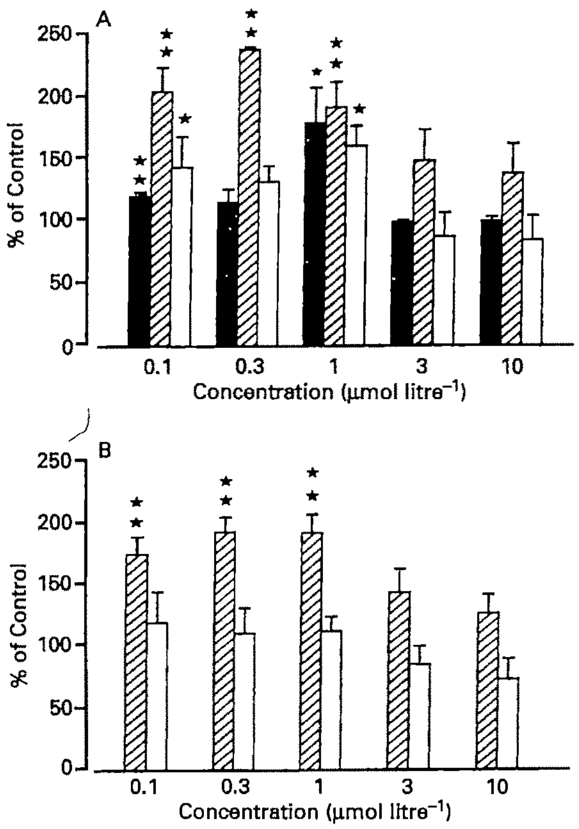


FIG. 4. A: Effects of neostigmine on EPP amplitude (□), time constant of decay (▨) and mean quantal content (■). B: Effects of neostigmine on MEPP amplitude (□), time constant of decay (▨). Columns represent means from 3–4 experiments on mouse triangularis sterni preparations; SE are shown by vertical bars. Significantly different from control: $^*P < 0.05$; $^{**}P < 0.01$.

The first negative deflection is associated with the inward movement of Na$^+$ ions at the nodes of Ranvier and heminode. The second negative deflection is the sum of the currents associated with the local circuit generated by outward movement of K$^+$ and the inward movement of Ca^{2+} at the nerve terminals (fig. 5A) [13, 14, 17]. Neostigmine 1–400 μmol litre^{-1} induced a concentration-dependent reduction in the second negative deflection of the perineural waveform, but had little or no effect on the first negative spike (fig. 5B). Similar effects with neostigmine were observed in the presence of a Ca^{2+}-free salt solution (fig. 5C).

DISCUSSION

Neostigmine is a powerful anticholinesterase and there is no reason to suppose that this is not the main basis of its facilitatory action on neuromuscular transmission. However, the present experiments show that it exerts an additional contributory action, albeit of lesser importance. Thus, in the presence of large concentrations of DFP which produced maximal antagonism of tubocurarine and which were therefore assumed to have produced maximal inhibition of junctional acetylcholinesterase, neostigmine continued to produce a further anticurare effect. Under these conditions, physostigmine and pyridostigmine failed to produce further antagonism of tubocurarine, suggesting that they do not share the extra action possessed by neostigmine. The action of neostigmine was clearly exerted on the transmission mechanism, because it had no effect on muscle contractions evoked by direct muscle stimulation.

Neostigmine produced the well documented increase in amplitude and duration of EPP and MEPP which are largely explicable in terms of its inhibitory action on acetylcholinesterase, as its ability to interact directly with postjunctional acetylcholine receptors requires very large concentrations [4–7]. In addition, the drug increased the quantal content of the EPP, which is attributed to an increase in

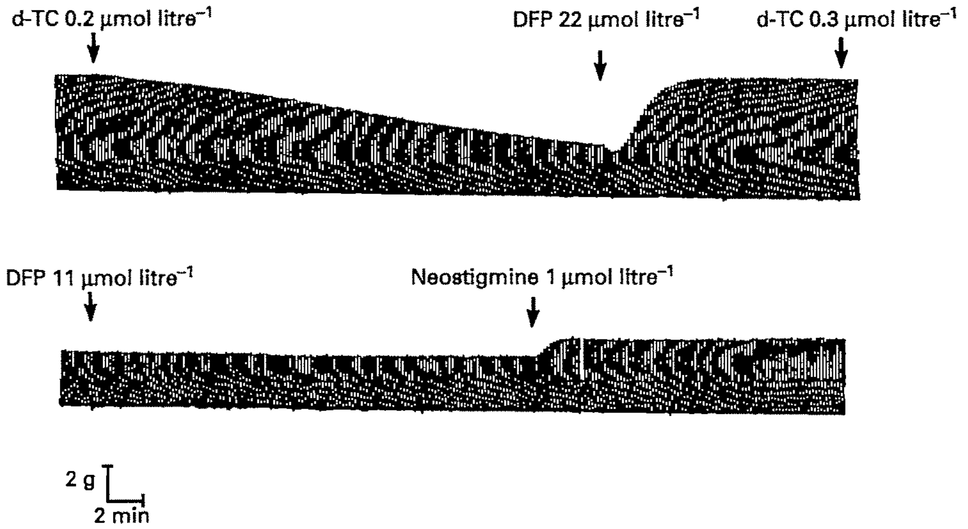


FIG. 3. Isolated phrenic nerve–hemidiaphgram preparation. Antagonism by DFP 22 μmol litre^{-1} of a 70% block of indirectly elicited twitch height induced by tubocurarine (d-TC) 0.2 μmol litre^{-1}. Then, a subsequent addition of tubocurarine 0.3 μmol litre^{-1} was used in order to induce, again, a 70% block of indirectly elicited twitch height. Under these conditions, a subsequent addition of DFP 11 μmol litre^{-1} failed to increase twitch height but the addition of neostigmine 1 μmol litre^{-1} could induce a further increase in twitch height. Experiments were carried out at room temperature (20–25 °C). Preparations were stimulated once every 10 s. Note that there is a 23-min gap in the recordings shown in the figure between the upper and lower panels.

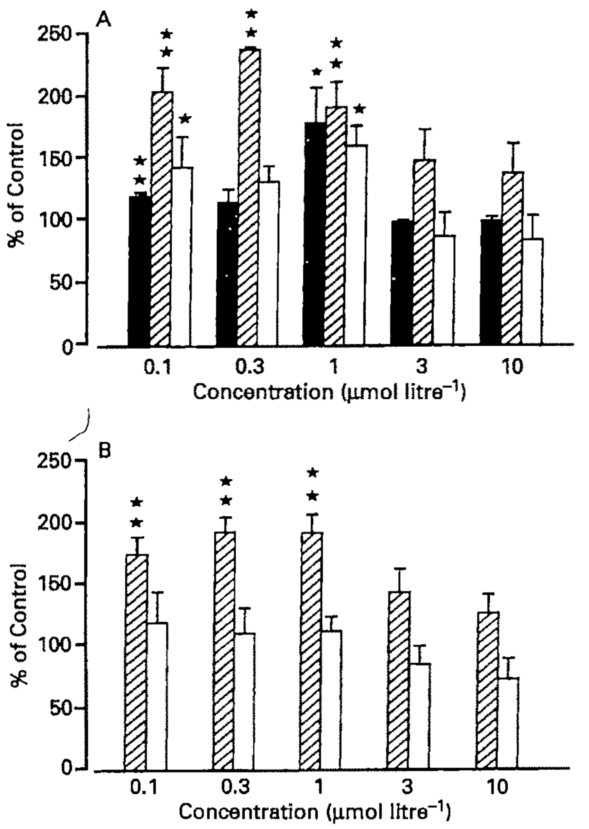


FIG. 4. A: Effects of neostigmine on EPP amplitude (☐), time constant of decay (▨) and mean quantal content (■). B: Effects of neostigmine on MEPP amplitude (☐), time constant of decay (▨). Columns represent means from 3–4 experiments on mouse triangularis sterni preparations; SE are shown by vertical bars. Significantly different from control: $*P < 0.05$; $**P < 0.01$.

The first negative deflection is associated with the inward movement of Na^+ ions at the nodes of Ranvier and heminode. The second negative deflection is the sum of the currents associated with the local circuit generated by outward movement of K^+ and the inward movement of Ca^{2+} at the nerve terminals (fig. 5A) [13, 14, 17]. Neostigmine 1–400 μmol litre^{-1} induced a concentration-dependent reduction in the second negative deflection of the perineural waveform, but had little or no effect on the first negative spike (fig. 5B). Similar effects with neostigmine were observed in the presence of a Ca^{2+}-free salt solution (fig. 5C).

DISCUSSION

Neostigmine is a powerful anticholinesterase and there is no reason to suppose that this is not the main basis of its facilitatory action on neuromuscular transmission. However, the present experiments show that it exerts an additional contributory action, albeit of lesser importance. Thus, in the presence of large concentrations of DFP which produced maximal antagonism of tubocurarine and which were therefore assumed to have produced maximal inhibition of junctional acetylcholinesterase, neostigmine continued to produce a further anticurare effect. Under these conditions, physostigmine and pyridostigmine failed to produce further antagonism of tubocurarine, suggesting that they do not share the extra action possessed by neostigmine. The action of neostigmine was clearly exerted on the transmission mechanism, because it had no effect on muscle contractions evoked by direct muscle stimulation.

Neostigmine produced the well documented increase in amplitude and duration of EPP and MEPP which are largely explicable in terms of its inhibitory action on acetylcholinesterase, as its ability to interact directly with postjunctional acetylcholine receptors requires very large concentrations [4–7]. In addition, the drug increased the quantal content of the EPP, which is attributed to an increase in stigmine to block acetylcholine-activated ion channels, in the same range of large concentrations as those reported here, has been described before [10, 23].

REFERENCES

1. Riker WF. Prejunctional effects of neuromuscular blocking and facilitatory drugs. In: Katz RL, ed. *Muscle Relaxants. Monographs in Anesthesiology, Vol. 3.* Amsterdam: North Holland Publishing Co., 1975; 59–102.
2. Miyamoto MD. The actions of cholinergic drugs on motor nerve terminals. *Pharmacological Reviews* 1978; **29**: 221–247.
3. Bowman WC, Gibb AJ, Harvey AL, Marshall IG. Prejunctional actions of cholinoceptor agonists and antagonists and of anticholinesterase drugs. In: Kharkevich DA, ed. *New Neuromuscular Blocking Agents, Handbook of Experimental Pharmacology, Vol. 79.* Berlin: Springer Verlag, 1986; 141–170.
4. Riker WF, Wescoe WC. The direct action of prostigmine on skeletal muscle; its relationship to the choline esters. *Journal of Pharmacology and Experimental Therapeutics* 1946; **88**: 58–66.
5. Pascuzzo GJ, Akaike A, Maleque MA, Shaw KP, Aronstam RS, Rickett DL, Albuquerque EX. The nature of the interactions of pyridostigmine with nicotinic acetylcholine receptor-ionic channel complex. I. Agonist, desensitizing, and binding properties. *Molecular Pharmacology* 1984; **25**: 92–101.
6. Sherby SM, Eldefrawi AT, Albuquerque EX, Eldefrawi ME. Comparison of the actions of carbamate anticholinesterases on the nicotinic acetylcholine receptor. *Molecular Pharmacology* 1985; **27**: 343–348.
7. Harvey AL, Dryden WF. The actions of some anticholinesterase drugs on skeletal muscle in culture. *Journal of Pharmacy and Pharmacology* 1974; **26**: 865–870.
8. Blaber LC, Christ DD. The actions of facilitatory drugs on the isolated tenuissimus muscle of the cat. *International Journal of Neuropharmacology* 1967; **6**: 473–484.
9. Provan SD, Miyamoto MD. Tetrahydroaminoacridine and physostigmine have opposing effects on probability of transmitter release at the frog neuromuscular junction. *Neuroscience Letters* 1991; **123**: 127–130.
10. Aracava Y, Deshpande SS, Rickett DL. The molecular basis of anticholinesterase actions on nicotinic and glutamatergic synapses. *Annals of the New York Academy of Sciences* 1987; **505**: 226–255.
11. McArdle JJ, Angaut-Petit D, Mallart A, Bournaud R, Faille L, Brigant JL. Advantages of the triangularis sterni muscle for investigation of synaptic phenomena. *Journal of Neurosciences Methods* 1981; **4**: 109–116.
12. Braga MFM, Harvey AL, Rowan EG. Effects of tacrine, velnacrine (HP029), suronacrine (HP128) and 3,4-diaminopyridine on skeletal neuromuscular transmission *in vitro*. *British Journal of Pharmacology* 1991; **102**: 909–915.
13. Mallart A. Electric current flow inside perineurial sheaths of mouse motor nerves. *Journal of Physiology (London)* 1985; **368**: 565–575.
14. Penner R, Dreyer F. Two different presynaptic calcium currents in mouse motor nerve terminals. *Pflügers Archiv, European Journal of Physiology* 1986; **406**: 190–197.
15. Anderson AJ, Harvey AL, Rowan EG, Strong PN. Effects of charybdotoxin, a blocker of Ca^{2+}-activated K^+ channels, on motor nerve terminals. *British Journal of Pharmacology* 1988; **95**: 1329–1335.
16. Dempster J. Computer analysis of electrophysiological signals. In: Frazer PJ, ed. *Microcomputers in Physiology: a Practical Approach.* Oxford: IRL Press, 1988; 51–93.
17. Brigant JL, Mallart A. Presynaptic currents in mouse motor endings. *Journal of Physiology (London)* 1982; **333**: 619–636.
18. Braga MFM, Rowan EG, Harvey AL, Bowman WC. On the potentiation of non-depolarizing blocking drugs by a previous injection of suxamethonium. (Abstract Discussion 4-h.) *Proceedings of the 4th International Neuromuscular Meeting, Montreal, Canada (1992).*
19. Hong SJ, Chang CC. Antagonism by tubocurarine and verapamil of the regenerative acetylcholine release from mouse motor nerve. *European Journal of Pharmacology* 1989; **162**: 11–17.
20. Harvey AL, Rowan EG. Actions of THA, 3,4 diaminopyridine, physostigmine and galanthamine on neuronal K^+ currents at a cholinergic nerve terminal. In: Giacobini E, Becker R, eds. *Current Research in Alzheimer Therapy.* New York: Taylor and Francis, 1988; 191–197.
21. Kordas M, Brzin M, Majcen Z. A comparison of the effect of cholinesterase inhibitors on end-plate current and on cholinesterase activity in frog muscle. *Neuropharmacology* 1975; **14**: 791–800.
22. Bradley RJ, Sterz R, Peper K. Agonist and inhibitory effects of pyridostigmine at the neuromuscular junction. *Brain Research* 1986; **376**: 199–203.
23. Wachtel RE. Comparison of anticholinesterases and their effects on acetylcholine-activated ion channels. *Anesthesiology* 1990; **72**: 496–503.

British Journal of Anaesthesia 1993; 70: 411–413

AN ALTERNATIVE METHOD OF INCREASING $P\text{CO}_2$ USING APNOEA AND CONTINUOUS POSITIVE AIRWAY PRESSURE

R. KARLSTEN AND S. ENGLESSON

SUMMARY

We have examined the use of continuous positive airway pressure (CPAP) and apnoeic oxygenation for restoration of spontaneous breathing at the end of anaesthesia after controlled ventilation. We studied 45 adult patients without a history of acute or chronic respiratory disturbances. Anaesthesia was induced with thiopentone or propofol and maintained with nitrous oxide and enflurane in oxygen. The patients were normocapnic during artificial ventilation. At the end of surgery, the lungs were ventilated for 5 min with oxygen and then given a CPAP of 8 cm H_2O. *Spontaneous ventilation was regained after a mean of 5 min and an arterial blood sample was obtained at the third breath. All patients were well oxygenated (*$P\text{O}_2$ *mean 43.5 kPa, range 21–76 kPa) when spontaneous ventilation started. The pH was close to 7.28 in most cases (mean 7.28, range 7.21–7.32), and* $P\text{CO}_2$ *varied in the range 6.6–9.9 kPa (mean 7.9 kPa). It is concluded that the method is safe with regard to oxygenation and acid–base balance.* (Br. J. Anaesth. 1993; **70**: 411–413)

KEY WORDS

Anaesthetic techniques: controlled ventilation, Ventilation: apnoeic oxygenation, CPAP.

At the end of general anaesthesia with artificial ventilation, spontaneous ventilation must be restored. During surgery, there is often a tendency to overventilate the lungs [1]. In order to stimulate spontaneous ventilation, three principal different methods have been used to increase $P\text{CO}_2$ at the end of anaesthesia [2]: to increase $P\text{CO}_2$ by decreasing alveolar ventilation; to bypass the soda-lime and depend on the metabolically produced carbon dioxide; and to supply exogenous carbon dioxide.

We have examined an alternative method of increasing arterial $P\text{CO}_2$ to greater than the apnoeic threshold in anaesthetized patients who have undergone normoventilation during surgery. The principle was to maintain oxygenation by apnoeic mass movement oxygenation [3] and continuous positive airway pressure (CPAP) and allow the patients themselves to restore $P\text{CO}_2$ to greater than the apnoeic threshold. The aim of the study was to evaluate the safety of this method with regard to oxygenation and acid–base balance and to determine the Pa_{CO_2} and pH at which spontaneous ventilation is regained after enflurane anaesthesia. We also intended to compare potential differences between patients in whom anaesthesia was induced with propofol and those given thiopentone.

PATIENTS AND METHODS

The study was approved by the Hospital Ethics Committee. Forty-five patients (25 male), mean age 39.9 yr (range 18–73 yr), without acute or chronic respiratory disturbances, undergoing elective ENT surgery under general anaesthesia, gave informed consent to participate in the study. They received our standard premedication with Ketogan (ketobemidone 5 mg and N,N-dimethyl-3,3-diphenyl-1-methylallylamine chloride 25 mg ml^{-1}) 0.5–1 ml and atropine 0.5 mg (patients younger than 65 yr) or glycopyrronium 0.2 mg (patients older than 65 yr) i.m.

The patients were allocated randomly to induction of general anaesthesia with propofol ($n = 19$) or thiopentone ($n = 26$) i.v., after which anaesthesia was maintained with 70% nitrous oxide and 1–2% enflurane. Fentanyl 0.05–0.1 mg was given at induction and supplementary doses (0.05–0.1 mg) were administered when needed. The total dose of fentanyl administered was 0–0.2 mg (mean 0.07 mg). Neuromuscular block was initiated with suxamethonium or vecuronium–pancuronium and if needed, maintained with incremental doses. Neuromuscular block was monitored using a peripheral nerve stimulator (Organon, Peripheral Nerve Stimulator, Neuro Technology, Houston, U.S.A.). Before insertion of the tracheal tube, the larynx and upper trachea were anaesthetized with 4% lignocaine solution. After intubation, the lungs were ventilated with an Excessobag anaesthesia ventilator (a bag-in-box device with a time-controlled injector) using a co-axial breathing system, with the same performance as the Bain [4]. The lungs were ventilated with a tidal volume of 0.01 litre kg^{-1} and a frequency of 12 b.p.m. with 0.1 litre kg^{-1} min^{-1} fresh gas flow during the first 10 min, reducing to 0.07 litre

---

Rolf Karlsten, M.D.; Sören Englesson, M.D., Ph.D.; Department of Anaesthesiology, University Hospital, S-751 85 Uppsala, Sweden. Accepted for Publication: September 17, 1992.

Correspondence to R.K.

TABLE I. *Arterial blood-gas tensions 25 min after adjustment of fresh gas flow to 70 ml kg^{-1} min^{-1} (mean (SD)).* n = 20

pH	$P\text{CO}_2$ (kPa)	$P\text{O}_2$ (kPa)	HCO_3 (mmol litre^{-1})	Base excess (mmol litre^{-1})
7.39 (0.04)	5.64 (0.60)	18.2 (6.0)	25.3 (1.9)	0.67 (2.1)

kg^{-1} min^{-1}. Oxygenation was monitored with pulse oximetry (Ohmeda, Biox 3740, Pulse Oximeter, Louisville, U.S.A.). In the first 20 patients (nine given propofol and 11 thiopentone), an arterial blood sample was obtained 25 min after the fresh gas flow was adjusted to 0.1 litre kg^{-1} min^{-1}. At the end of surgery, after antagonism of neuromuscular block, the lungs were ventilated with 100% oxygen for 5 min with a fresh gas flow 1 litre min^{-1} less than the sum of nitrous oxide in oxygen used during anaesthesia, to eliminate most of the nitrous oxide. Thereafter, the ventilator was set at CPAP 8 cm H_2O. When spontaneous breathing began, an arterial blood sample was obtained at the third breath and analysed for blood-gas tensions and acid–base state, at the gas laboratory of the Department of Clinical Physiology using an ABL II blood-gas machine (Radiometer, Copenhagen)

Statistics

All results are presented as means (SD). Statistical evaluation was performed using Student's *t* test. Linear regression was analysed for the relationship between Pa_{CO_2} and pH against the duration of apnoea.

RESULTS

Anaesthesia lasted between 45 min and 2 h 15 min. During surgery and at restoration of spontaneous breathing, there was no difference in Pa_{O_2}, Pa_{CO_2} or pH between the patients who received propofol, compared with those given thiopentone. Consequently, the results in all patients are presented together in tables I and II.

During anaesthesia, mean pH was 7.39 (SD 0.04) and Pa_{CO_2} 5.6 (0.6) kPa (table I).

The mean Pa_{CO_2} at which spontaneous ventilation was regained was 7.9 (0.8) kPa and the pH was 7.28 (0.02); all patients had increased Pa_{O_2} (43.5 (13.5) kPa (range 21–76 kPa)). The mean time for apnoea and CPAP was 5 (2.2) min.

The correlation between Pa_{CO_2} and pH *vs.* duration of apnoea is presented in figure 1.

DISCUSSION

At the end of general anaesthesia with artificial ventilation there are three major methods of allowing resumption of spontaneous breathing [2]: to let the patient regain consciousness, which may restart spontaneous breathing at a value of $P\text{CO}_2$ less than the apnoeic threshold [1, 2, 5]; to increase $P\text{CO}_2$ to greater than the apnoeic threshold [1, 2]; and to administer a non-specific stimulant [2].

One possible disadvantage with the first of these methods is that, after tracheal extubation, the patient might hypoventilate when left unstimulated, as in the recovery room [6]. The influence of external stimulation was reported in an early study by Utting and Gray [7], in which no respiratory depressant drugs were used and breathing resumed at decreased $P\text{CO}_2$. They concluded that stimuli arising from the periphery were sufficient to cause initiation of breathing. They also reported that, if topical analgesia had been applied to the larynx and trachea before intubation, there was frequently a delay in resumption of spontaneous ventilation.

It is inevitable that, after operation, $P\text{CO}_2$ increases to greater than the apnoeic threshold [2]. If the patient is allowed to breathe air after operation, there is a risk of hypoxaemia when the patient hypoventilates in order to refill the carbon dioxide stores [8]. Even if supplementary oxygen is delivered, hypoventilation may cause atelectasis, with hypoxaemia in the later postoperative period. For these reasons, it seems sensible to increase the $P\text{CO}_2$ at the end of anaesthesia.

There are also three methods of increasing $P\text{CO}_2$ to greater than apnoeic threshold [1, 2]. The first is to decrease alveolar ventilation at the end of surgery [1, 2]. This is a slow method and has the added risk of hypoxaemia because of alveolar hypoventilation and development of alveolar collapse [1]. The second method is to cause rebreathing of carbon dioxide by removing the soda-lime canister. This method is a little faster than the first [2]. The third and quickest method is to add carbon dioxide gas to the breathing system [1, 2]. This increases $P\text{CO}_2$ to the desired value in less than 1 min [1]. However, the addition of a carbon dioxide flowmeter to the system introduces several hazards. Death and permanent cerebral damage have been reported secondary to accidental high flows of carbon dioxide gas [9, 10].

Our method of increasing $P\text{CO}_2$ by using apnoea and CPAP induced spontaneous breathing in all patients while the Pa_{O_2} was well within safe margins. Emergence was smooth, as spontaneous breathing was restored and the trachea extubated before full consciousness was regained. With modern postoperative care there is usually no reason to waken the patient fully in the operating theatre, and it may be preferable to allow the patient to regain consciousness slowly in the postoperative ward. Because $P\text{CO}_2$ has been increased to greater than the apnoeic threshold, this may reduce the risk of hypoventilation during transport from operating

TABLE II. *Arterial blood-gas tensions at the third breath after CPAP and time from onset of CPAP and apnoea to restoration of spontaneous breathing (mean (SD)).* n = 45

pH	$P\text{CO}_2$ (kPa)	$P\text{O}_2$ (kPa)	HCO_3 (mmol litre^{-1})	Base excess (mmol litre^{-1})	CPAP (min)
7.28 (0.02)	7.88 (0.83)	43.5 (12.7)	24.1 (1.7)	0.50 (1.8)	5.00 (2.2)

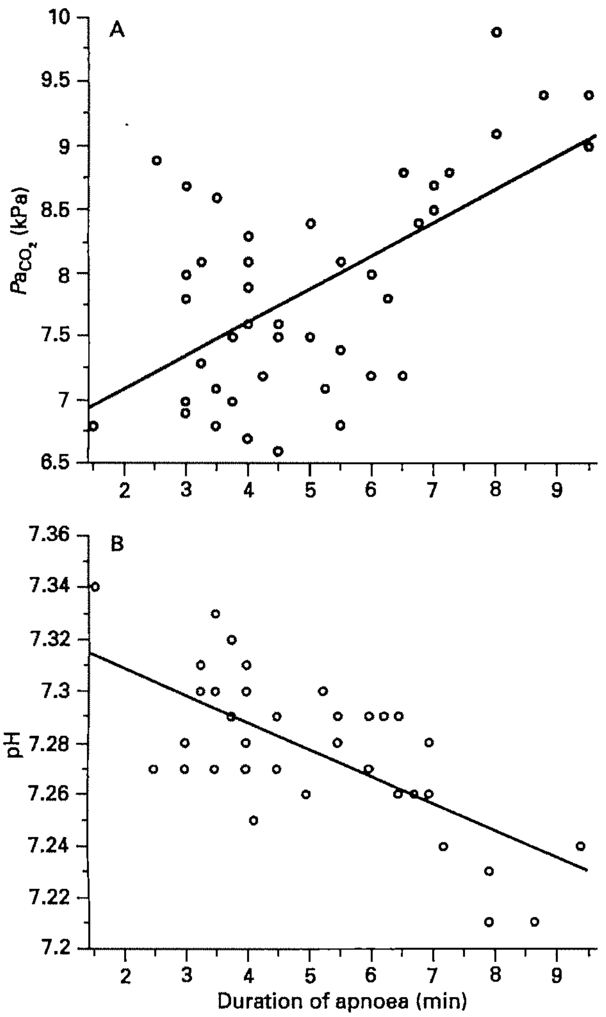


FIG. 1. A: Relationship between the duration of apnoea and Pa_{CO_2} at the third breath after initiation of spontaneous breathing. $r^2 = 0.34$, $n = 45$. B: Relationship between the duration of apnoea and pH at the third breath after initiation of spontaneous breathing. $r^2 = 0.49$, $n = 45$.

theatre and in the postoperative ward. However, Salvatore, Sullivan and Papper have shown that, if the lungs have been hyperventilated during surgery (the duration of the hyperventilation averaged 2.75 h), this might not be true, as the patients are depleted of body stores of carbon dioxide and have a deficit of carbon dioxide even after apnoea [8]. Recovery from such depletion is achieved by relative hypoventilation in the first 1 h after operation, with consequent risk of hypoxaemia [8, 11]. Even if supplementary oxygen is administered during this period, relative hypoventilation may induce atelectasis. For this reason, it seems sensible not to hyperventilate the lungs during anaesthesia.

In three of our patients, apnoea lasted 9–9.5 min and breathing started at a pH of 7.21–7.24 (fig. 1). All three patients had a low frequency of ventilation (4–5 b.p.m.) and their pupils were small, indicating opioid effects. These effects were antagonized easily with naloxone.

Severe hypercapnia is not necessarily fatal, provided adequate oxygenation is maintained [12, 13]. However, a long duration of apnoea might indicate that the patient is suffering from respiratory depression. This observation has led us to set a limit on the duration of apnoea as 8 min, after which we look for causes of respiratory depression (fig. 1).

Edelist and Osorio [14] have shown that the drive to resume ventilation in passively hyperventilated dogs and humans is the result of restoration of CSF pH to normal even though the blood is well oxygenated, extremely alkalotic and hypocapnic. In addition, it takes time to establish equilibrium between blood and brain PCO_2, and therefore it is difficult to extrapolate from blood PCO_2 to the actual respiratory centre pH [15]. For this reason, the results in the present study should not be thought of as "respiratory threshold values". Frumin, Epstein and Cohen [16] showed that severe respiratory acidosis (without hypoxia) produced by apnoea lasting more than 30 min could be tolerated easily by lightly anaesthetized normal patients, with complete recovery. That study also indicated that the serum concentration of potassium did not change markedly during apnoea. Holmdahl [3] studied the effects of 6 min of apnoeic diffusion oxygenation and found that all patients remained well oxygenated and that pH decreased by 0.14–0.18.

REFERENCES

1. Nunn JF. Carbon dioxide cylinders on anaesthetic apparatus. *British Journal of Anaesthesia* 1990; **65**: 155–156.
2. Ivanov SD, Nunn JF. Methods of elevation of PCO_2 for restoration of spontaneous breathing after artificial ventilation of anaesthetized patients. *British Journal of Anaesthesia* 1969; **41**: 28–37.
3. Holmdahl MH. Pulmonary uptake of oxygen, acid–base metabolism, and circulation during prolonged apnoea. *Acta Chirurgica Scandinavica* 1956; (Suppl.): 212.
4. Jonsson LO, Zetterström H. The influence of the respiratory flow pattern on rebreathing in Mapleson A and D circuits. *Acta Anaesthesiologica Scandinavica* 1987; **31**: 174–178.
5. Fink BR. Influence of cerebral activity in wakefulness on regulation of breathing. *Journal of Applied Physiology* 1961; **16**: 15–20.
6. Miller RD. Anesthesia for the elderly. In: Miller RD, eds. *Anesthesia*. New York: Churchill Livingstone, 1986; 1801–1818.
7. Utting JE, Gray C. The initiation of respiration after anaesthesia accompanied by passive pulmonary hyperventilation. *British Journal of Anaesthesia* 1962; **34**: 785–789.
8. Salvatore AJ, Sullivan SF, Papper EM. Postoperative hypoventilation and hypoxemia in man after hyperventilation. *New England Journal of Medicine* 1969; **280**: 467–470.
9. Utting JE, Gray TC, Shelley FC. Human misadventures in anaesthesia. *Canadian Anaesthetists Society Journal* 1979; **26**: 472–478.
10. Razis PA. Carbon dioxide—a survey of its use in anaesthesia in the U.K. *Anaesthesia* 1989; **44**: 348–351.
11. Sullivan SF, Patterson RW, Teychenne J. Posthyperventilation hypoxia. *Journal of Applied Physiology* 1967; **22**: 431–435.
12. Prys-Roberts C, Smith WDA, Nunn JF. Accidental severe hypercapnia during anaesthesia. *British Journal of Anaesthesia* 1967; **39**: 257–267.
13. Prys-Roberts C. Hypercapnia. In: Gray TC, Nunn JF, Utting JE, eds. *General Anaesthesia*. London: Butterworths, 1980; 435–460.
14. Edelist G, Osorio A. Postanesthetic initiation of spontaneous ventilation after passive hyperventilation. *Anesthesiology* 1969; **31**: 222–227.
15. Hanks EC, Ngai SH, Fink BR. The respiratory threshold for carbon dioxide in anesthetized man. *Anesthesiology* 1961; **22**: 393–397.
16. Frumin MJ, Epstein RM, Cohen G. Apneic oxygenation in man. *Anesthesiology* 1959; **20**: 789–798.

British Journal of Anaesthesia 1993; 70: 414–418

VENTILATORY EFFECTS OF MORPHINE, PETHIDINE AND METHADONE IN CHILDREN

K. HAMUNEN

SUMMARY

The ventilatory effects of single i.v. doses of morphine 0.1 mg kg^{-1}, pethidine 0.67 mg kg^{-1} and methadone 0.1 mg kg^{-1} were compared after ophthalmic surgery in an open, randomized study in 30 children aged 3–8 yr. Ventilatory changes after each drug had distinctive profiles, with appreciable individual variation. Acutely, the decrease in ventilatory frequency was greater with pethidine and methadone than with morphine. The acute decrease in oxygen saturation was greater with methadone and pethidine than with morphine. Methadone produced a greater and longer lasting increase in end-tidal carbon dioxide and greater decrease in end-tidal oxygen than morphine or pethidine. Changes in end-tidal carbon dioxide and oxygen concentrations and saturation were most transient after pethidine and of longest duration after methadone. No child developed apnoea or hypoventilation requiring assistance. (Br. J. Anaesth. 1993; **70**: 414–418)

KEY WORDS

Anaesthesia: paediatric. Analgesics: methadone, morphine, pethidine. Pain: postoperative.

Depression of ventilation is an inevitable effect of all mu receptor agonists. The principal mechanism involves decreased responsiveness of the respiratory centres to increases in carbon dioxide tension. Nevertheless, because of technical difficulties and ethical issues, only a few paediatric studies on the ventilatory effects of i.v. opioids have been carried out. Morphine is an opioid fundamental to the treatment of pain in both children and adults, and a standard drug against which other analgesics are compared in clinical trials. When given for pain, morphine rarely causes clinically important ventilatory depression in children [1–3], although ventilatory frequency is decreased in both children and adults [4, 5]. Pethidine is used often in the management of paediatric pain and premedication, even though it has few, if any, documented advantages over morphine. The analgesic efficacy and side effects of pethidine are comparable to those of morphine, but it has a shorter duration of action [6]. During recent years, methadone has been advocated for management of postoperative pain, and in some countries it is fundamental to the treatment of cancer pain in children [7]. The analgesic effect of methadone is comparable to that of morphine, but of considerably longer duration [8–12].

Analysis of end-tidal gases is a non-invasive, continuous and sensitive method of measurement of the ventilatory variables [13, 14]. The aim of this study was to compare the effects of equianalgesic i.v. single doses of morphine hydrochloride (referred to subsequently as morphine), pethidine and methadone given after operation, on ventilatory frequency, end-tidal carbon dioxide and oxygen concentrations and peripheral arteriolar oxygen saturation in children.

PATIENTS AND METHODS

The study was an open, randomized, single-dose design approved by the local Ethics Committee. Parental informed consent was obtained for all children. Children were excluded if they had severe cardiovascular or respiratory disease, hepatic or renal insufficiency, any congenital or genetic disorder possibly causing atypical opioid response or kinetics, or were severely overweight.

We studied 30 children aged 3–10 yr, undergoing elective ophthalmic surgery. Patients were allocated to groups according to the day of birth (1–10 days of month morphine, 11–20 days pethidine and 21–30 methadone). Premedication comprised oral liquid flunitrazepam 0.1 mg kg^{-1} (maximum 2 mg). Anaesthesia was induced with thiopentone 5 mg kg^{-1}. Patients were intubated and ventilated to normocapnia using a Siemens–Elema 900 ventilator (Siemens, Sweden). Anaesthesia was maintained with 66% nitrous oxide and 1–2 vol% halothane in oxygen. Relaxation was produced with pancuronium and the degree of block was monitored with a transcutaneous nerve stimulator. At the end of surgery, residual neuromuscular block was antagonized with neostigmine and glycopyrronium. No analgesics were given during anaesthesia.

After transfer to the recovery room, patients were given additional oxygen for 20 min. Non-invasive arterial pressure measurement, ECG (for heart rate) and pulse oximetry (peripheral arteriolar oxygen

---

KATRI HAMUNEN, B.M., Department of Ophthalmology, University of Helsinki, Helsinki, Finland. Address for correspondence: Department of Ophthalmology, Helsinki University Hospital, SF-02900 Helsinki, Finland. Accepted for Publication: April 14, 1992.

TABLE I. *Characteristics of the patients and duration of anaesthesia (mean (SD) [range])*

	Morphine ($n = 10$)	Pethidine ($n = 10$)	Methadione ($n = 10$)
Sex (M/F)	4/6	7/3	4/6
Age (yr)	6.7 [3.8–8.9]	6.8 [4.9–8.3]	7.1 [3.2–10.0]
Weight (kg)	22.5 (4.9) [18.6–32.0]	26.9 (10.2) [17.9–52.9]	25.6 (8.4) [17.2–44.5]
Height (cm)	121 (11) [107–140]	123 (9) [112–138]	122 (13) [101–145]
Duration (min)	66 (32) [25–140]	60 (8) [52–73]	84 (27) [42–125]

TABLE II. *Predrug values and AUC values (mean (SD)) with 95% confidence interval (CI) for the ventilatory variables after morphine, pethidine or methadone in children. *** Significant difference between methadone and the two other groups (P < 0.001)*

	Morphine ($n = 10$)	Pethidine ($n = 10$)	Methadone ($n = 10$)
Ventilatory frequency (b.p.m.)			
Predrug	25.6 (4.1)	26.8 (4.6)	24.7 (3.1)
AUC	−6.06	−4.85	−6.19
95% CI	1.74	1.26	1.82
E'_{CO_2} (%)			
Predrug	6.7 (0.4)	7.0 (0.5)	6.7 (0.4)
AUC	−0.39	−0.44	0.31***
95% CI	0.25	0.27	0.20
E'_{O_2} (%)			
Predrug	12.9 (0.7)	14.1 (0.5)	14.5 (0.7)
AUC	0.80	0.56	−0.50***
95% CI	0.43	0.38	0.23
Sp_{O_2} (%)			
Predrug	95.4 (1.4)	94.7 (1.4)	96.0 (0.9)
AUC	−0.08	1.13	−0.75
95% CI	1.56	0.67	0.97

saturation, Sp_{O_2}) were monitored using a Cardiocap CMO (Datex, Helsinki, Finland). End-tidal carbon dioxide (E'_{CO_2}) and oxygen (E'_{O_2}) concentrations and ventilatory frequency were monitored using a Capnomac (Datex, Helsinki, Finland). To collect end-tidal gas samples, a small plastic tube was inserted in one of the patient's nostrils, to which topical anaesthetic cream EMLA (Astra, Sweden) had been applied during anaesthesia. At the end of anaesthesia, the nose and pharynx were cleared by suction to ensure free air flow.

Thirty minutes after discontinuation of anaesthesia (10 min after discontinuation of additional oxygen) the patients were given single i.v. doses of morphine 0.1 mg kg^{-1}, pethidine 0.67 mg kg^{-1} or methadone 0.1 mg kg^{-1} as prophylactic analgesic treatment. If the patient was assessed to have pain during the observation period, a rescue analgesic (diclofenac 1 mg kg^{-1} i.v.) was given as indicated. Ventilatory measurements were continued for 2.5 h after administration of the drugs.

Data were collected as a mean value of every 10 s to a central monitoring computer for later analysis. Data were plotted every 2 min for the first 16 min, every 5 min for the next 40 min and then every 10 min for the remainder of the study. All side effects and adverse reactions during the observation period were recorded.

Data were analysed with Systat 5.0, operating system DOS 3.31 run on Compaq Portable 386 [15]. For statistical comparison, all ventilatory and cardiovascular variables were expressed as change from the starting value immediately before administration of the study drugs. Area under the curve (AUC) was calculated for the curves produced by plotting the following variables against time: ventilatory frequency (AUC_{VF}), end-tidal carbon dioxide ($AUC_{E'_{CO_2}}$), end-tidal oxygen ($AUC_{E'_{O_2}}$), peripheral arteriolar oxygen saturation ($AUC_{Sp_{O_2}}$), heart rate (AUC_{HR}), and systolic (AUC_{SAP}) and diastolic (AUC_{DAP}) arterial pressures. All values for AUC were calculated using the linear trapezoidal rule and then normalized to compensate for differences in follow-up time. AUC was used because, as a cumulative index, it provides a better global estimate of a variable than any single value. Acute effects were evaluated by examining the maximum changes of the respective ventilatory and cardiovascular variables. One-way analysis of variance and Student's *t* test for unpaired data were used to compare AUC values between groups. A significant difference was accepted at $P < 0.05$.

RESULTS

Characteristics of the patients in the treatment groups are shown in table I. Predrug values and AUC values with 95% confidence interval (CI) for the ventilatory variables after each drug are shown in table II. Follow-up time was 150 min in all 10 patients in the morphine and methadone groups and seven patients in the pethidine group; three patients in the pethidine group were followed up for 140 min.

After administration of the analgesics, the acute decrease (0–4 min) in ventilatory frequency was significantly greater with pethidine and methadone than with morphine ($P < 0.05$). There was no difference between pethidine and methadone in this respect. AUC_{VF} values were the same in the study groups. Based on the mean ventilatory frequency curves, ventilatory frequency decreased sharply after pethidine and methadone in contrast with morphine, reaching a minimum at 6 and 21 min, respectively (fig. 1).

There was no significant difference in the E'_{CO_2} values between morphine and pethidine. $AUC_{E'_{CO_2}}$ for methadone differed significantly from those of morphine and pethidine ($P < 0.001$). Maximum mean E'_{CO_2} occurred at 12, 6 and 8 min with morphine, pethidine and methadone, respectively. It was significantly ($P < 0.001$) greater with methadone than with morphine or pethidine. Based on the mean E'_{CO_2} curves, E'_{CO_2} values remained increased for 31, 14 and 81 min after morphine, pethidine and methadone, respectively (fig. 1). In individual patients, the greatest E'_{CO_2} values were 6.6–7.6% (mean 7.1 (SD 0.4)%) in the morphine group, 6.7–8.6% (7.5 (0.6)%) in the pethidine group and 7.3–8.4% (8.0 (0.4)%) in the methadone group. The magnitude of increase in E'_{CO_2} individual patients was not related to the predrug E'_{CO_2} or duration of anaesthesia.

$AUC_{E'_{O_2}}$ for methadone was significantly smaller ($P < 0.001$) than that of morphine or pethidine.

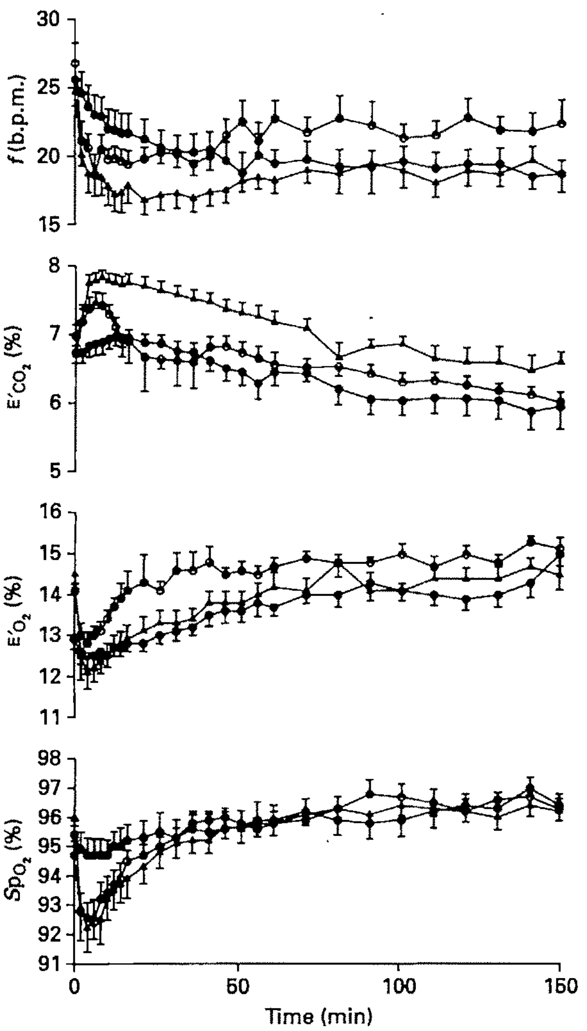


FIG. 1. Mean (SE) ventilatory frequency (*f*), end-tidal carbon dioxide concentrations (E'_{CO_2}), end-tidal oxygen concentrations (E'_{O_2}) and peripheral arteriolar oxygen saturations (Sp_{O_2}) in children after i.v. administration of morphine 0.1 mg kg^{-1} (●), pethidine 0.67 mg kg^{-1} (○) or methadone 0.1 mg kg^{-1} (▲).

Minimum values of the mean E'_{O_2} curves differed significantly ($P < 0.03$) between drugs, being smallest with methadone and greatest with morphine. They occurred at 4 min in all treatment groups. Recovery of the mean E'_{O_2} curves to predrug values occurred at 26, 16 and 61 min with morphine, pethidine and methadone, respectively (fig. 1). The acute decrease in Sp_{O_2} was significantly greater ($P < 0.05$) with methadone than with morphine or pethidine. Sp_{O_2} values differed between morphine and pethidine only at 4 min ($P < 0.036$). $AUC_{Sp_{O_2}}$ values did not differ between the groups. Mean Sp_{O_2} curves recovered to predrug values at 26 min after morphine, 21 min after pethidine and 71 min after methadone (fig. 1).

No child needed additional oxygen or ventilatory support after the administration of the drugs. Criteria for administration of additional oxygen or ventilatory assistance were Sp_{O_2} less than 90 % or ventilatory frequency less than 8 b.p.m. For all three drugs, the time, duration and magnitude of ventilatory changes varied considerably between individuals. Changes in heart rate and arterial pressure were clinically insignificant and did not differ between treatment groups. During the day of operation, nine patients given morphine, nine given pethidine and seven given methadone needed additional analgesic. A second dose of the same opioid was given for severe pain to one patient in the pethidine group (at 2 h 50 min after the first dose), and two patients in the methadone group (at 2 h 45 min and at 1 h 15 min after the first dose). After the administration of the second dose of opioid, ventilatory values of the patient were excluded from the data analysis from the moment of administration. Duration of sleep and analgesia after the drugs and side effects are shown in table III.

TABLE III. *Duration of sleep and analgesia, need of rescue analgesic and side effects on the operation day, after morphine, pethidine and methadone in children. Duration of analgesia = time to administration of rescue analgesic. Mean* (SD) [*range*]

	Morphine ($n = 10$)	Pethidine ($n = 10$)	Methadone ($n = 10$)
Duration of sleep after operation (min)	85 (27) [40–130]	77 (22) [54–110]	107 (32) [25–135]
Patients needing rescue analgesic (No.)	9	9	7
Duration of analgesia after drug (min)	191 (142) [60–525]	171 (166) [63–570]	211 (156) [75–480]
Nausea or vomiting (No. patients)	3	3	3
Urinary retention (No. patients)	1	1	1

DISCUSSION

In this study, anaesthetic and fluid management, positioning of the child and timing of drug administration were standardized in order to permit comparisons. Opioids were not used for premedication or during anaesthesia. Diclofenac was chosen for the primary rescue analgesic because it does not affect ventilation and has been shown to be effective for pain in children [16]. This management is not optimal for prevention of postoperative pain, and the opioid-induced ventilatory depression is superimposed upon recovery from anaesthesia, but this design allows measurements of ventilatory changes in a calm and co-operative child, breathing room air.

The smaller control value of E'_{O_2} in the morphine group compared with those in the two other groups, and the small differences of E'_{CO_2} and E'_{O_2} values from values predicted by the alveolar air equation, may be related to errors in measurements. The relatively high baseline ventilatory frequency and E'_{CO_2} value probably reflect residual halothane effects. However, the mean ventilatory frequency in each group decreased promptly in response to the i.v. opioids. In general, ventilatory frequency proved to be an insensitive indicator of hypoventilation. The greatest E'_{CO_2} value in this study, 8.6 % in a patient in the pethidine group, was associated with a ventilatory frequency of 17 b.p.m. and a temporary decrease in Sp_{O_2} to 87 %. In the methadone group, two patients had maximal E'_{CO_2} values of 8.2–8.3 % with ventilatory frequencies of 14–17 b.p.m. and Sp_{O_2} 91–92%, respectively, but another patient had a maximum E'_{CO_2} value of 8.2% with ventilatory frequency 27 b.p.m. and Sp_{O_2} saturation 90%. Delay between the decreases in E'_{O_2} and Sp_{O_2}, reported in adult patients [14], did not occur in this study, possibly because of the shorter circulation time in young children compared with adults.

The analgesic potencies of morphine, pethidine and methadone have not been compared in children. In the present study it was not possible to assess equianalgesia, but the mean time to rescue analgesia in this study corresponds with the expected duration of analgesia of the three drugs [6]. The doses studied were based on clinical practice of administering i.m. pethidine 1 mg kg^{-1} and morphine 0.15 mg kg^{-1} to children. Morphine and methadone were regarded as equal in potency [6, 10]. It is not known if the ventilatory depressant effects of truly equianalgesic doses of morphine, pethidine and methadone differ in magnitude. However, this study has shown a clear difference in the time course of ventilatory changes.

In adults, pethidine has been shown to produce slight but rarely clinically significant decreases in ventilatory frequency [17–19] or changes in ventilatory volumes or arterial gas tensions with no decrease in ventilatory frequency [20, 21]. In newborn infants, pethidine produces less ventilatory depression than morphine [22]. In older children, ventilatory frequencies were similar after administration of morphine and pethidine [23]. In the present study, acute changes in ventilatory frequency, E'_{CO_2} and Sp_{O_2} after pethidine were steeper, but of shorter duration than after morphine. The shorter effect of pethidine is in agreement with data in adults [6].

In common with previous studies, this study suggests that methadone produces slightly more ventilatory depression than morphine, but the risk of significant hypoventilation is small with the doses used [10–12, 24]. However, larger doses or accumulation of methadone during long-term administration may produce significant ventilatory depression [11, 24, 25]. In our study, methadone produced more prolonged changes in ventilation than morphine or pethidine. This is consistent with the longer duration of analgesia and slower elimination of methadone compared with those of morphine or pethidine [8, 12, 26]. As previously reported in adults [26], the maximal increase in E'_{CO_2} occurred more rapidly after methadone than after morphine. This is consistent with the greater lipid solubility of methadone [27].

ACKNOWLEDGEMENTS

I am grateful to Dr Eeva-Liisa Maunuksela, M.D., PH.D., for guidance during preparation of the study and Dr Klaus Olkkola, M.D., PH.D., for statistical analysis and production of the figures in this paper. I would also like to thank R. N. Riitta Lindelöf. The Paulo Foundation provided a grant.

REFERENCES

1. Lynn AM, Opheim KE, Tyler DC. Morphine infusion after pediatric cardiac surgery. *Critical Care Medicine* 1984; **12**: 863–866.
2. Beasley SW, Tibbals J. Efficacy and safety of continuous morphine infusion for postoperative analgesia in the pediatric surgical ward. *Australian and New Zealand Journal of Surgery* 1987; **57**: 233–237.
3. Hendrickson M, Myre L, Johnson DG, Matlak ME, Black RE, Sullivan JJ. Postoperative analgesia in children: A prospective study of intermittent intramuscular injection versus continuous intramuscular infusion of morphine. *Journal of Pediatric Surgery* 1990; **25**: 185–191.
4. Miser AW, Miser JS, Clark BS. Continuous intravenous infusion of morphine sulfate for control of severe pain in children with terminal malignancy. *Journal of Pediatrics* 1980; **96**: 930–932.
5. Clyburn PA, Rosen M, Vickers MD. Comparison of the respiratory effects of i.v. infusions of morphine and regional analgesia by extradural block. *British Journal of Anaesthesia* 1990; **64**: 446–449.
6. Jaffe JH, Martin WR. Opioid analgesics and antagonists. In: Gilman A, Goodman LS, Rall TW, Murad F, eds. *The Pharmacological Basis of Therapeutics*. New York: Macmillan, 1985; 491–531.
7. Maunuksela E-L, Saarinen UM, Lähteenoja K-M. Prevalence and management of terminal pain in children with cancer: 5-year experience in Helsinki, Finland. In: Tyler DC, Crane EJ, eds. *Advances in Pain Research and Therapy*. New York: Raven Press, 1990; 383–390.
8. Berde CB, Sethna NF, Holzman RS, Reidy P. Pharmacokinetics of methadone in children and adolescents in the perioperative period. *Anesthesiology* 1987; **67**: A519.
9. Berde CB, Beyer JE, Bournaki M-C, Levin CR, Sethna NF. Comparison of morphine and methadone for prevention of postoperative pain in 3- to 7-year-old children. *Journal of Pediatrics* 1991; **119**: 136–141.
10. Gourlay GK, Wilson PR, Glynn CJ. Pharmacodynamics and pharmacokinetics of methadone during the perioperative period. *Anesthesiology* 1982; **57**: 458–467.
11. Gourlay GK, Willis RJ, Wilson PR. Postoperative pain control with methadone: Influence of supplementary methadone doses and blood concentration–response relationships. *Anesthesiology* 1984; **61**: 19–26.
12. Gourlay GK, Willis RJ, Lamberty J. A double-blind comparison of the efficacy of methadone and morphine in postoperative pain control. *Anesthesiology* 1986; **64**: 322–327.
13. Linko K, Paloheimo M. Monitoring of the inspired and end-tidal oxygen, carbon dioxide, and nitrous oxide concentrations: Clinical applications during anesthesia and recovery. *Journal of Clinical Monitoring* 1989; **5**: 149–156.
14. Nikki P, Bahr M, Paloheimo MPJ. Comparison of non-invasive respiratory and arterial blood gas analysis. A recovery room study on acute respiratory depression. *Scandinavian Journal of Clinical Laboratory Investigations* 1990; **50** (Suppl. 203): 213–216.
15. Wilkinson L. *Systat: The System for Statistics*. Evanston, IL: Systat Inc., 1990.
16. Todd PA, Sorkin EM. Diclofenac sodium: A reappraisal of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy. *Drugs* 1988; **35**: 244–285.
17. Muneyuki M, Ueda Y, Urabe N, Takeshita H, Inamoto A. Postoperative pain relief and respiratory function in man. *Anesthesiology* 1968; **29**: 304–313.
18. Davenport HT, Al-Khudairi D, Cox PN, Wright BM. Continuous subcutaneous pethidine for routine postoperative analgesia. *Annals of the Royal College of Surgeons of England* 1985; **67**: 379–381.
19. Welchew EA, Hosking J. Patient-controlled postoperative analgesia with alfentanil. *Anaesthesia* 1985; **40**: 1172–1177.
20. Orkin LR, Egge RK, Rovenstine EA. Effect of nissentil, meperidine and morphine on respiration in man. *Anesthesiology* 1955; **16**: 699–707.
21. Keats AS, Girgis KZ. Respiratory depression associated with relief of pain by narcotics. *Anesthesiology* 1968; **29**: 1006–1013.
22. Way WL, Costley EC, Way EL. Respiratory sensitivity of the newborn infant to meperidine and morphine. *Clinical Pharmacology and Therapeutics* 1965; **6**: 454–461.
23. O'Hara M, McGrath PJ, D'Astous J, Vair CA. Oral morphine versus injected meperidine (Demerol) for pain relief in children after orthopedic surgery. *Journal of Pediatric Orthopedics* 1987; **7**: 78–82.

24. Berde CB, Holzman RS, Sethna NF, Dickerson RB, Brustowicz RM. A comparison of methadone and morphine for postoperative analgesia in children and adolescents. *Anesthesiology* 1988; **69**: A768.
25. Ettinger DS, Vitale PJ, Trump DL. Important clinical pharmacologic considerations in the use of methadone in cancer patients. *Cancer Treatment Reports* 1979; **63**: 457–459.
26. Gourlay GK, Cherry DA, Cousins MJ. A comparative study of the efficacy and pharmacokinetics of oral methadone and morphine in the treatment of severe pain in patients with cancer. *Pain* 1986; **25**: 297–312.
27. Kaufman JJ, Semo NM, Koski WS. Microelectrometric titration measurement of the pK_a's and partition and drug distribution coefficients of narcotics and narcotic antagonists and their pH and temperature dependence. *Journal of Medicinal Chemistry* 1975; **18**: 647–655.

British Journal of Anaesthesia 1993; 70: 419–422

COMPARISON OF MIDAZOLAM WITH PROPOFOL FOR SEDATION IN OUTPATIENT BRONCHOSCOPY

M. CRAWFORD, J. POLLOCK, K. ANDERSON, R. J. GLAVIN, D. MACINTYRE AND D. VERNON

SUMMARY

We have compared sedation for fibreoptic bronchoscopy provided by incremental doses of midazolam with that provided by a computer-controlled infusion of propofol. These two methods were compared in terms of operator and patient acceptability, anxiolysis, effects on systolic arterial pressure and oxygen saturation. Tests were made also of memory and motor reactions, before and 60 min after the end of the procedure. Acceptability to operators and patients was high in both groups. There were no significant differences between the groups in systemic arterial pressure or anxiolysis. Oxygen saturation decreased in both groups (propofol group median 83% (range 69–95%); midazolam group median 86% (range 77–95%)) (ns). The median recovery time was 5 min (range 5–10 min) in the propofol group and 10 min (range 5–40 min) in the midazolam group ($P < 0.01$*). Memory and motor reaction times 60 min after the end of the procedure did not differ from baseline in the propofol group, but were significantly impaired in the midazolam group.* (Br. J. Anaesth. 1993; **70**: 419–422)

KEY WORDS

Anaesthetic techniques: bronchoscopy, i.v. sedation. Anaesthetics, intravenous: propofol. Hypnotics, benzodiazepines: midazolam.

Flexible fibreoptic bronchoscopy is a technique used commonly by respiratory physicians in the management of patients with many types of respiratory disease. However, it is associated with both morbidity and mortality. Most deaths and complications associated with bronchoscopy arise from the procedure itself, but at least five deaths and up to 50% of the major life-threatening complications have been related to the sedative regimen used [1].

Systemic arterial desaturation occurs during bronchoscopy, and may be caused by several factors, including topical anaesthesia [2, 3], sedation [4], partial airway obstruction [2], abnormal distribution of ventilation [2] and reflex response to bronchoscopy and lavage [5]. If the desaturation persists after the end of the procedure, this is most likely to result from oversedation, as the other factors produce only transient changes.

Persistence of sedation beyond the end of the procedure is undesirable in the outpatient, as this may result in detention of the patient in hospital. Although bronchoscopy may be performed without sedation, one study has reported that 60% of the patients who did not receive sedation found this very unpleasant or intolerable [6].

The ideal agent for sedation in bronchoscopy should provide amnesia, anxiolysis and analgesia, such that the patient is comfortable, co-operative with the bronchoscopist and willing, if necessary, to return for a repeat procedure [1].

We have attempted to ascertain how well these conditions are achieved with a low-dose infusion of propofol. We have compared the sedation and recovery associated with propofol with that associated with midazolam, which is commonly used to provide sedation for bronchoscopy.

PATIENTS AND METHODS

After obtaining Ethics Committee approval, we studied 42 patients undergoing fibreoptic bronchoscopy, with their written informed consent. They were allocated randomly to receive either propofol or midazolam. Patients and bronchoscopists were blinded to the type of sedation used. Patients were excluded if they were currently receiving, or had recently taken, a benzodiazepine.

Patients' weight was recorded, with baseline measurements of heart rate, arterial pressure and oxygen saturation. Memory was tested using E. K. Warrington Memory Recognition Tests. These are psychological tests used to assess short-term recall of 25 words and faces, generating a score (maximum 25) for each. Motor performance was assessed using a Motor Reaction Timer. This is a device whereby the patient switches off a series of coloured lights which are activated by the assessor, and the machine resolves the movement into a decision time and a movement time, both in seconds. Each patient completed a 10-cm visual analogue scale (VAS) for

---

M. CRAWFORD*, F.F.A.R.C.S.I., J. POLLOCK, F.R.C.ANAES., R. J. GLAVIN, F.R.C.ANAES. (Department of Anaesthesia); K. ANDERSON, M.D., M.R.C.P., D. MACINTYRE, M.R.C.P., D. VERNON, M.R.C.P. (Department of Respiratory Medicine); Victoria Infirmary, Glasgow. Accepted for Publication: October 28, 1992.

*Present address, for correspondence: Department of Anaesthesia, Western Infirmary, Dumbarton Road, Glasgow.

anxiety, and was assessed in performance of a finger–nose test.

Each patient received 4% nebulized lignocaine 4 ml, followed by topical lignocaine 10 mg to each nostril and to the oropharynx. Further 2-ml increments of 4% lignocaine were administered via the bronchoscope by the operator as required. Three bronchoscopists (two consultants and one senior registrar) performed all of the procedures. All bronchoscopies were performed with the patient in a semi-recumbent position.

Propofol and midazolam were administered via a 20-gauge cannula sited in the dorsum of the hand. Propofol was infused, and the rate of infusion controlled by the Psion Organiser–Ohmeda 9000 Infusion Pump system devised by Kenny and White [7]. An initial target blood concentration was selected of 1.5 $\mu g\ ml^{-1}$ for a period of 2 min, and this was increased incrementally each 1 min by 0.25 $\mu g\ ml^{-1}$ until 2.0 $\mu g\ ml^{-1}$, and thereafter in 0.1-$\mu g\ ml^{-1}$ increments each 1 min until adequate sedation was achieved. Those patients receiving midazolam were given initially a 2-mg bolus, and after 2 min were given increments of 1 mg min^{-1} until adequate sedation was achieved. Patients and operators were blinded to the drug administered, as follows: each patient was connected to a propofol infusion via a 200-cm manometer line with a three-way tap at the i.v. cannula. These were then covered with a large surgical sheet. The infusion device was activated in all patients, but was not programmed to deliver in the patients receiving midazolam; in these patients, the midazolam was given at the level of the three-way tap. Patients receiving propofol were given sterile water at intervals to blind the sedation further. The sedation score described by MacKenzie and Grant [8] was used and the patients were judged to be sedated adequately by the bronchoscopist when they had closed eyes but were rousable to command.

An anaesthetist was present throughout each procedure, and was responsible for administration of the sedation, and for monitoring of the patient. Each patient was monitored by sphygmomanometer and by Ohmeda Biox 3700 pulse oximeter. Arterial pressure was recorded at intervals of 2 min, and pulse oximetry data were recorded using an interface to a Psion Organiser POS 200 hand-held computer. Oxygen was administered by nasal catheter if oxygen saturation decreased to less than 85%. Pulse oximetry was continued until 60 min after the end of the procedure, and the data recorded were subsequently retrieved and analysed manually.

Recovery was judged to have occurred when there was return of spontaneous eye opening, correct recall of date of birth and ability to perform the finger–nose test without past pointing. These tests were repeated at 5, 10, 15, 20, 30, 40 and 60 min after the end of the procedure, until recovery occurred. The Memory Recognition Tests, Motor Reaction Tests and Visual Analogue Scale for anxiety were repeated 60 min after the end of the procedure, at which point study of the patients finished.

Patients completed a questionnaire 60 min after the procedure. The bronchoscopists also completed a questionnaire. All patients were given a set of written postoperative instructions and were accompanied home by a relative or friend.

TABLE I. *Patient characteristics (mean (range or SD)).* *P < *0.05* *(Student's* t *test for the means of two groups)*

	Midazolam		Propofol
Age (yr)	63.5 (48–85)		63.9 (38–81)
Weight (kg)	54.85 (10.44)	*	63.65 (10.63)
Systolic AP (mm Hg)	140 (31.1)		135 (23.3)
Heart rate (beat min^{-1})	85.8 (13.4)		84.5 (13.1)
Sp_{O_2} (%)	95.2 (2.3)		95 (2.1)

TABLE II. *Time to sedation and total duration of procedure (mean (SD))*

	Midazolam	Propofol
Time to sedation (min)	4.2 (2.6)	4.7 (2.1)
Duration of procedure (min)	17.4 (4.3)	20.8 (10.4)

Data were analysed by chi-square test, Student's *t* test for the means of two samples, and Wilcoxon's Rank Sum Test as appropriate. $P < 0.05$ was accepted as statistically significant.

RESULTS

At the conclusion of the study, there were 21 patients in each group, but it became apparent that there were more males in the propofol group ($n = 16$) than in the midazolam group ($n = 9$) ($P < 0.05$, χ^2 test with Yates' correction). This was reflected in the greater mean weight in the propofol group (63.65 (SD 10.63) kg), than in the midazolam group (54.85 (10.44) kg) ($P < 0.02$, Student's *t* test for the means of two groups).

Otherwise, the two groups were similar in age and baseline recordings of arterial pressure, heart rate and oxygen saturation (table I). There were four patients of ASA grade II and 17 of ASA grade III in the midazolam group, and five of ASA grade II with 16 of ASA grade III in the propofol group.

The time to sedation and total duration of procedure were similar in the two groups (table II).

The median dose of midazolam was 6 mg (0.0063 mg kg^{-1} min^{-1}) (range 3–18 mg). The patient who received 18 mg had a particularly high alcohol intake; the next greatest dose was 10 mg. The median dose of propofol was 155 mg (0.1171 mg kg^{-1} min^{-1}); this equates with an average anaesthetic induction dose. The range of doses was 71–420 mg; the patient who received 420 mg underwent a procedure which lasted 60 min; and the next greatest dose was 350 mg.

Extra sedation was requested by the bronchoscopist for seven patients in the midazolam group and four patients in the propofol group. Three patients in the midazolam group became unresponsive to command during the procedure, as did five patients in the propofol group; in the latter patients, there was rapid return of an appropriate level of sedation on reduction of the rate of infusion of propofol. However, in the patients in the midazolam group, the oversedation persisted until the end of the procedure.

There were no differences between the two groups

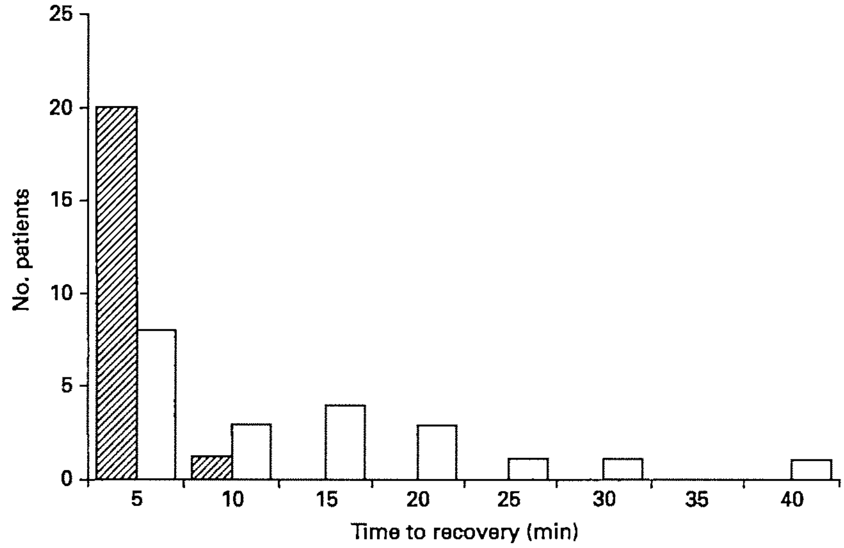


FIG. 1. Times to recovery from sedation in the propofol (▨) and midazolam (☐) groups. Significant difference between groups ($P < 0.01$; Wilcoxon rank sum test).

TABLE III. *Results of memory and motor reaction tests (mean (SD)).* *P < 0.05; ***P < 0.001 *(Student's* t *test for the means of two samples)*

	Before bronchoscopy		After bronchoscopy
Propofol group			
Words	20.9 (2.45)		20.6 (2.9)
Faces	19.4 (3.24)		18.3 (3.3)
Decision time (s)	0.55 (0.3)		0.5 (0.3)
Movement time (s)	0.33 (0.2)		0.31 (0.2)
Midazolam group			
Words	21.3 (2.32)	***	16.2 (3.2)
Faces	19.5 (3.17)	***	14.3 (2.8)
Decision time (s)	0.47 (0.08)	*	0.54 (0.14)
Movement time (s)	0.31 (0.09)	***	0.48 (0.14)

in mean greatest or mean least systolic arterial pressure measured during the procedure.

Oxygen saturation decreased during the procedure in every patient in both groups. Median least oxygen saturation in the propofol group was 83% (range 69–95%); that in the midazolam group was 86% (range 77–95%) (ns). There were no statistically significant differences in mean oxygen saturation between the two groups at the time recovery was said to have occurred, or at 60 min after the end of the procedure. Additionally, in both groups at each of these times, mean oxygen saturation was not significantly different from baseline. Seven patients in each group required administration of oxygen during the procedure. Four patients in each group suffered desaturation after sedation, but before introduction of the bronchoscope, and in each this was by 10 or more percentage points from the baseline saturation. Each of these patients had baseline saturations of > 95% breathing air, and the desaturation continued after insertion of the bronchoscope.

Median time to recovery was twice as long in the midazolam group (10 min, range 5–40 min) as that in the propofol group (median 5 min, range 5–10 min) ($P < 0.01$, Wilcoxon rank sum test). Twenty of the propofol patients had recovered by 5 min and only one patient required 10 min (fig. 1).

There were no statistically significant differences between the two groups in preoperative assessment of memory or of motor reaction times. Similarly, there were no differences between baseline measurements in the propofol group and those taken 60 min after the end of the bronchoscopy. However, in the midazolam group these tests produced results at 60 min which were significantly worse than baseline (table III).

Postoperative VAS anxiety scores were comparable in each group, and were substantially smaller than those recorded before sedation began.

The results of a questionnaire completed by the bronchoscopists after the end of the procedure revealed similar levels of satisfaction for both sedative regimens. The results of the patient questionnaire showed similar levels of satisfaction in each group, 100% of patients finding the procedure to be comfortable. Two patients in the propofol group and one patient in the midazolam group recalled insertion of the bronchoscope, but none of these patients was distressed.

No patient who received propofol complained of pain as a result of infusion of this drug, although this information was not specifically sought.

DISCUSSION

The blood concentrations of propofol predicted by this delivery system have been validated during its use in general anaesthesia [7, 9]. Despite the apparent complexity of this system, we have shown that the time taken to achieve adequate sedation was comparable to the time taken using incremental doses of midazolam (the recommended method of administration of midazolam [10]). Using an incremental technique, the median dose of midazolam was approximately twice the dose advised by Roche in the product Data Sheet for a patient of the mean weight in the midazolam group [10]. Using incremental intervals of 1 min, three patients in the midazolam group became unresponsive to command. Incremental intervals of 2 min may therefore be more appropriate for this drug in order to reduce the incidence of oversedation; this measure might reduce the acceptability of midazolam in procedures lasting an average of 20 min.

It is well known that propofol may cause hypotension, when given as a bolus or by infusion to produce anaesthesia. However, it has been shown to be devoid of cardiorespiratory side effects when used in small doses to provide sedation [8]. Sedation with midazolam may cause hypotension [11]; both drugs had no adverse effects on arterial pressure in the current study.

Both propofol and midazolam may produce respiratory depression [4]. In this study, equal numbers of patients in each group suffered severe arterial desaturation as a result of sedation alone, before the effect of the bronchoscope and washing solutions. Median least oxygen saturation recorded during the procedure was smaller in the propofol group than in the midazolam group, although this was not statistically significant. However, it has been shown that, when midazolam is used in combination with fentanyl (as may be more usually the case in sedation for bronchoscopy), these two agents act synergistically rather than additively [12]. Potential for greater desaturation than that shown in this study would seem to be present with this commonly used combination of agents.

The results of our tests of memory and motor reactions show clearly that, when midazolam is used for sedation in this procedure, there remains significant impairment of memory and motor reactions 60 min after the end of the procedure. A recent study using a battery of tests of recovery has shown that central nervous system impairment may persist for at least 3.5 h after flumazenil antagonism of midazolam sedation, although patients may have a subjective feeling of alertness which may have dangerous consequences [13]. This is certainly undesirable in outpatients, and highlights the unsuitability of this "short-acting" benzodiazepine for sedation in procedures of short duration. The results of the memory and motor reaction tests for patients in the propofol group were different from those of the midazolam group; at 60 min, they were not significantly different from the baseline, pre-sedation results. With particular reference to the motor reaction tests, it can be seen that both mean decision time and mean movement time were shorter at 60 min after the end of the procedure, although this was not statistically significant. It would appear that these patients had recovered sufficiently to be able to recall their pre-sedation experience of the motor reaction timer and to improve on their performance with it.

We have demonstrated that, if used cautiously and if dosage is titrated to effect, it is possible to use midazolam alone for sedation in fibreoptic bronchoscopy, without detriment to oxygen saturation after the end of the procedure. However, its effects on memory and motor performance make it, in our opinion, less suitable for use in the outpatient.

In a major review of sedation for fibreoptic bronchoscopy [1], the authors stated: "no single agent provides amnesia, anxiolysis and analgesia, so a combination of drugs is necessary." We consider that an infusion of propofol, after topical lignocaine anaesthesia, provides conditions which come close to this ideal. In addition, the rapid onset and short duration of action of propofol allow rapid changes in depth of sedation and swift recovery without the need for expensive antagonist agents. These are particularly important features because, even with the cautious administration used in both groups of this study, it is possible to exceed the limits of sedation and approach anaesthesia. This possibility leads us to recommend that the administration of sedation for endoscopic procedures should be the responsibility of a medical practitioner experienced in both management of the airway and the use of the drugs given.

The evanescent nature of the effects of propofol may make this the most appropriate drug for use in the "high-risk" patient, in whom ease of change of depth of sedation, rapid recovery and cardiovascular stability are essential requirements. Hypoxaemia undoubtedly still occurs during bronchoscopy with this agent, but sedation is not the only cause, and it may be prevented easily by administration of oxygen via a nasal catheter.

REFERENCES

1. Shelley MP, Wilson P, Norman J. Sedation for fibreoptic bronchoscopy. *Thorax* 1989; **44**: 769–775.
2. Salisbury BG, Metzger LF, Altose MD, Stanley NN, Cherniak NS. Effect of fibreoptic bronchoscopy on respiratory performance in patients with chronic airways obstruction. *Thorax* 1975; **30**: 441–446.
3. Peacock AJ, Benson-Mitchell R, Godfrey R. Effect of fibreoptic bronchoscopy on pulmonary function. *Thorax* 1990; **45**: 38–41.
4. Bell GD, Reeve PA, Moshiri M, Morden A, Coady T, Stapleton PJ, Logan RF. Intravenous midazolam: a study of the degree of oxygen desaturation occurring during upper gastrointestinal endoscopy. *British Journal of Clinical Pharmacology* 1987; **23**: 703–708.
5. Dubrowsky C, Awe RJ, Jenkins DE. The effect of bronchofiberscopic examination on oxygenation status. *Chest* 1975; **67**: 137–140.
6. Rees PJ, Hay JG, Webb JR. Premedication for fibreoptic bronchoscopy. *Thorax* 1983; **38**: 624–627.
7. Kenny GNC, White M. A portable computerised infusion system for propofol. *Anaesthesia* 1990; **45**: 692–693.
8. MacKenzie N, Grant IS. Propofol for intravenous sedation. *Anaesthesia* 1987; **42**: 3–6.
9. White M, Kenny GNC. Intravenous propofol anaesthesia using a computerised infusion system. *Anaesthesia* 1990; **45**: 204–209.
10. Roche Products Ltd. *Midazolam (Hypnovel) Data Sheet.* Welwyn Garden City: Roche, 1989.
11. Committee on Safety of Medicines. Midazolam (Hypnovel) —respiratory depression and hypotension. *Current Problems* 1985; No. 14.
12. Ben-Shlomo I, Abd-el-Khalim H, Ezry J, Zohar S, Tverskoy M. Midazolam acts synergistically with fentanyl for induction of anaesthesia. *British Journal of Anaesthesia* 1990; **64**: 45–47.
13. Andrews PJD, Wright DJ, Lamont MC. Flumazenil in the outpatient: a study following midazolam as sedation for upper gastrointestinal endoscopy. *Anaesthesia* 1990; **45**: 445–448.

British Journal of Anaesthesia 1993; 70: 423–427

COMPARISON OF INFUSION RATES OF THREE I.V. ANAESTHETIC AGENTS FOR INDUCTION IN ELDERLY PATIENTS

M. C. BERTHOUD, G. A. McLAUGHLAN, I. J. BROOME, P. D. HENDERSON, J. E. PEACOCK AND C. S. REILLY

SUMMARY

We have compared the effect of different rates of injection of 2.5% thiopentone, 0.5% methohexitone and 0.2% etomidate for induction of anaesthesia in 90 premedicated, elderly patients. The agents were administered by infusion pump at rates of 1200 ml h^{-1}, 600 ml h^{-1} and 300 ml h^{-1}, respectively until anaesthesia was induced as judged by loss of verbal contact with the patient. The times for induction were significantly greater with the slower infusion rates (thiopentone 41 s, 57 s and 91 s ($P < 0.001$); methohexitone 44 s, 62 s and 84 s ($P < 0.01$); etomidate 48 s, 59 s and 87 s ($P < 0.001$)). The doses were significantly smaller ($P < 0.001$) with the slower infusion rates for all three agents (thiopentone 5.0, 3.7 and 2.8 mg kg^{-1}; methohexitone 1.00, 0.75 and 0.56 mg kg^{-1}; etomidate 0.26, 0.15 and 0.11 mg kg^{-1}). For each drug there was no significant difference in induction characteristics, oxygen saturation, heart rate or mean arterial pressure, at the different infusion rates. (Br. J. Anaesth. 1993; **70**: 423–427)

KEY WORDS

Age factors: elderly. Anaesthetic techniques: i.v. infusion. Anaesthetics, intravenous: etomidate, methohexitone, thiopentone.

In a previous study, we have shown that a slower rate of administration of propofol for induction of anaesthesia in elderly patients resulted in smaller dose requirements [1]. Using an Ohmeda 9000 syringe pump to control accurately the rate of administration of propofol at 5, 10 and 20 ml min^{-1}, we demonstrated that the dose requirements for induction could be reduced markedly, and that this was accompanied by a significant reduction in the incidence of apnoea, and the degree of hypotension. In the present study, we have examined the effect of infusion rate on the induction dose requirement and plasma concentrations of thiopentone, methohexitone and etomidate. We have also examined the effect of infusion rate on induction characteristics, such as the incidence of pain on injection or apnoea, and on arterial pressure, oxygen saturation and heart rate.

PATIENTS AND METHODS

We studied 90 patients of class ASA I or II, aged 60 yr or older, undergoing elective body surface or urological surgery and who did not require tracheal intubation as part of the planned anaesthetic technique. Patients were excluded if they had clinical evidence of respiratory, cardiac, hepatic, renal or endocrine disease, uncontrolled hypertension, previous adverse response to general anaesthesia, body weight more than 20% greater than ideal, or were receiving any medication likely to influence the course of anaesthesia or haemodynamic response.

The study was approved by the local Ethics Committee, and written informed consent was obtained from all patients. One investigator collected data for each agent: thiopentone (M.B.), methohexitone (G.McL.) and etomidate (I.B.). Temazepam 20 mg was given orally 1 h before induction of anaesthesia. In the anaesthetic room an i.v. cannula was inserted into each arm, one for the administration of drugs and the other for venous sampling. Patient monitoring consisted of non-invasive arterial pressure (Dinamap), ECG and pulse oximetry.

All patients were asked to report any discomfort on i.v. injection of the anaesthetic drug and were asked also to keep talking as long as they could in response to open-ended questioning after the start of injection. They were then given fentanyl 0.75 μg kg^{-1} i.v., 5 min before the induction of anaesthesia. Patients were allocated randomly to one of three groups to receive the selected drug by infusion at rates of 1200, 600 or 300 ml h^{-1} (equivalent to 5, 10, or 20 ml min^{-1}) for induction of anaesthesia, using an Ohmeda 9000 syringe pump. The induction agents were used in concentrations calculated to administer approximately equipotent doses over a 30-s period at the 1200-ml h^{-1} infusion rate. The concentrations of drugs used were thiopentone 25 mg ml^{-1}, etomidate 2 mg ml^{-1} and methohexitone

---

MIREILLE C. BERTHOUD, B.M., F.R.C.ANAES.; GILLIAN A. McLAUGHLAN, M.B., CH.B., F.R.C.ANAES.; IAN J. BROOME, M.B., CH.B., F.R.C.ANAES.; PETER D. HENDERSON; JOHN E. PEACOCK, M.B., CH.B., F.R.C.ANAES.; CHARLES S. REILLY, M.D., F.R.C.ANAES.; Department of Anaesthesia, University of Sheffield Medical School, Beech Hill Road, Sheffield S10 2RX. Accepted for Publication: October 16, 1992.

TABLE I. *Patient data (mean (range or* SD)). *$^*P < 0.05$ compared with those receiving 300 ml h^{-1} of same drug*

	Infusion rate for induction (ml h^{-1})		
	300	600	1200
Age (yr)			
Thiopentone	68.5 (62–77)	78.5 (68–87)*	72.7 (62–85)
Methohexitone	76.4 (64–88)	75.4 (63–86)	69.5 (61–79)*
Etomidate	76.0 (64–88)	72.4 (62–88)	71.2 (62–86)
Weight (kg)			
Thiopentone	66.4 (10.9)	64.5 (10.7)	69.1 (11.2)
Methohexitone	72.7 (10.0)	72.5 (12.2)	71.3 (11.0)
Etomidate	67.7 (16.8)	71.3 (15.9)	63.3 (16.8)
ASA (I:II)			
Thiopentone	6:4	3:7	8:2
Methohexitone	5:5	6:4	6:4
Etomidate	4:6	5:5	6:4
Sex (M:F)			
Thiopentone	6:4	5:5	4:6
Methohexitone	7:3	7:3	6:4
Etomidate	5:5	4:6	3:7

5 mg ml^{-1}, which would result in doses of 3.6 mg kg^{-1}, 0.28 mg kg^{-1} and 0.70 mg kg^{-1} respectively, for a 70-kg individual over a 30-s infusion period. Anaesthesia was defined as loss of verbal contact with the patient, at which point the infusion was discontinued. For maintenance of anaesthesia, the patients breathed a mixture of 66 % nitrous oxide in oxygen, with enflurane according to clinical requirements, via a mask and a Mapleson D system.

The rate of infusion, the duration of induction and the total induction dose were recorded. Cardiovascular measurements were made before and 4 min after fentanyl, at the end of induction, and at 2-min intervals for 10 min after induction. Peripheral oxygen saturation was recorded at the same times using a pulse oximeter. Periods of apnoea greater than 30 s were treated by intermittent positive pressure ventilation and periods of oxygen desaturation to 90 % or less were treated with increased inspired oxygen concentrations. The incidence of any period of apnoea greater than 30 s, any pain on injection and the presence of excitatory or other side effects were noted.

Blood samples were obtained at 2, 5 and 10 min after induction. The serum was extracted and frozen to −20 °C within 30 min for subsequent analysis. Drug analysis was performed using HPLC with u.v. detection. The internal standards were flunitrazepam for thiopentone [2, 3], hexobarbitone for methohexitone [4] and propoxate for etomidate [5]. The coefficients of variation for analysis of thiopentone were 2.84 % at 1 μg and 3.7 % at 10 μg, of methohexitone were 2.98 % at 1 μg and 3.26 % at 10 μg, and of etomidate were 3.05 % at 120 ng and 0.85 % at 460 ng. The lower limit of detection for thiopentone was 1.0 μg, for methohexitone was 0.2 μg and for etomidate was 25 ng.

Statistical analysis was performed using Analysis of Variance with Tukey's HSD test to compare patient data, induction times, induction doses and serum concentrations of drugs. Repeat Measures Analysis of Variance was used for arterial pressure, heart rate and oxygen saturation. Chi-square analysis was used to compare the incidence of apnoea and pain on injection.

RESULTS

The patients receiving thiopentone 600 ml h^{-1} for induction were significantly older than those receiving 300 ml h^{-1}. The patients receiving methohexitone 1200 ml h^{-1} were significantly younger than those receiving 300 ml h^{-1}. There were no other significant differences between infusion rate groups (table I).

All patients were anaesthetized successfully using the regimen described. The patients receiving the induction agents at 1200 ml h^{-1} had mean induction times of 40–48 s; the time was 84–90 s in those receiving the induction agent at 300 ml h^{-1} (table II). The differences in induction time between the different infusion rate groups was significant for all agents ($P < 0.001$ for thiopentone and etomidate; $P < 0.01$ for methohexitone). Those patients receiving 1200 ml h^{-1} had mean induction doses of 5.0 mg kg^{-1} for thiopentone, 1.0 mg kg^{-1} for methohexitone and 0.26 mg kg^{-1} for etomidate, decreasing to 2.8 mg kg^{-1}, 0.56 mg kg^{-1} and 0.11 mg kg^{-1}, respectively, in patients receiving 300 ml h^{-1}. These differences between induction rate groups were significant for all three agents ($P < 0.001$).

For all three induction agents, the serum concentration decreased with time and with decreasing infusion rate (fig. 1). The difference in thiopentone concentration was significant at 5 min ($P = 0.002$) and 10 min ($P = 0.003$); that in methohexitone concentration was significant at 10 min ($P = 0.016$).

The area under the concentration–time curve (AUC) from 2 min to 10 min was calculated using the trapezoidal rule for each patient (table II). Those patients receiving the faster infusions had larger AUC. These differences were significant in patients receiving thiopentone ($P = 0.016$) and methohexitone ($P = 0.025$), but not in those receiving etomidate. The correlation coefficients of dose against AUC were calculated for each patient: $r = 0.671$ for thiopentone, $r = 0.682$ for methohexitone and $r = 0.607$ for etomidate (significant at $P < 0.001$).

No patient receiving thiopentone or methohexitone experienced pain on injection. Of the

TABLE II. *Induction times, doses and AUC (mean (SD)). Significant differences between infusion rate groups:* *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$

	Infusion rate for induction (ml h^{-1})		
	300	600	1200
Dose (mg kg^{-1})			
Thiopentone***	2.8 (0.4)	3.7 (0.4)	5.0 (1.0)
Methohexitone***	0.56 (0.12)	0.75 (0.21)	1.00 (0.18)
Etomidate***	0.11 (0.03)	0.15 (0.04)	0.26 (0.05)
Induction time (s)			
Thiopentone***	90.8 (19.3)	57.4 (10.5)	40.8 (6.7)
Methohexitone**	83.8 (31.6)	62.2 (20.5)	43.6 (4.2)
Etomidate***	89.6 (15.0)	59.0 (7.4)	47.7 (7.1)
AUC at 10 min (μg ml^{-1} min)			
Thiopentone*	60.4 (25.0)	71.9 (14.9)	86.8 (35.6)
Methohexitone*	16.3 (6.9)	21.6 (20.7)	26.9 (13.4)
Etomidate	1.08 (0.38)	1.48 (1.05)	2.08 (1.16)

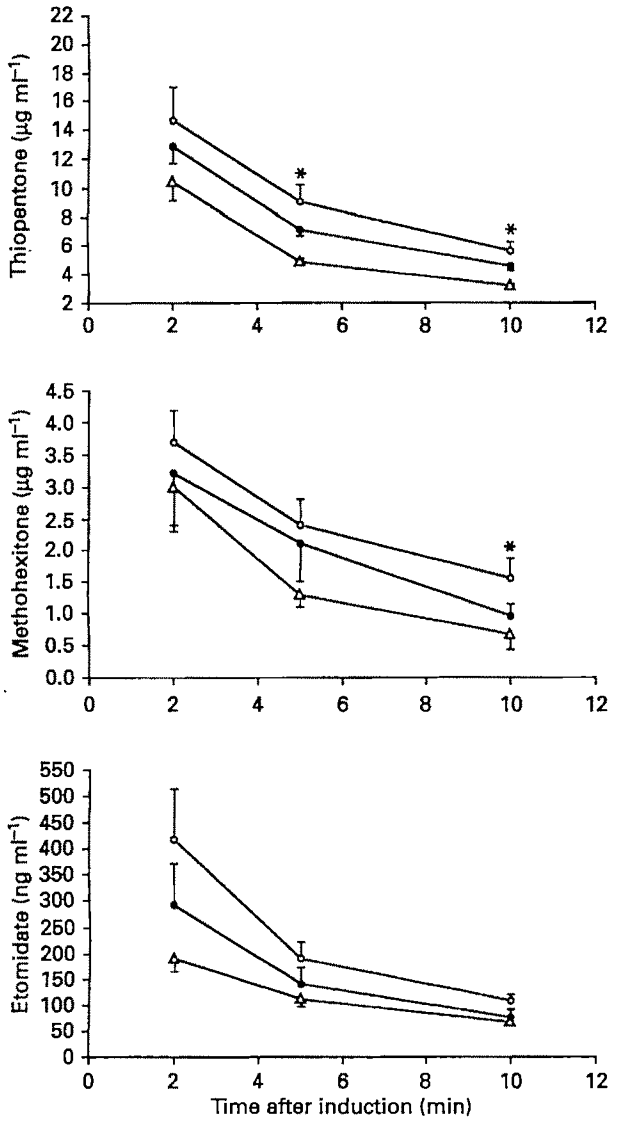


FIG. 1. Effect of infusion rate on plasma drug concentrations (mean, SE). △ = 300 ml h^{-1}; ● = 600 ml h^{-1}; ○ = 1200 ml h^{-1}. *$P < 0.05$ between infusion rates.

TABLE III. *Incidence and duration of apnoea and incidence of pain on injection*

	Infusion rate for induction (ml h^{-1})		
	300	600	1200
Incidence of apnoea > 30 s			
Thiopentone	3	7	4
Methohexitone	2	2	5
Etomidate	1	3	2
Mean duration of apnoea (s)			
Thiopentone	75	118	93
Methohexitone	52	52	61
Etomidate	—	40	32
Incidence of pain on injection			
Thiopentone	nil	nil	nil
Methohexitone	nil	nil	nil
Etomidate	2	7	5

patients receiving etomidate, two in the 300-ml h^{-1} group, seven in the 600-ml h^{-1} and five in the 1200-ml h^{-1} group experienced pain on injection. One patient receiving each of the faster rates of infusion complained that the pain was severe (table III).

There was no statistical difference between induction rate groups, for each infusion rate, with respect to the incidence of apnoeic episodes more than 30 s in duration and the mean duration of apnoea (table III).

From baseline mean of 96.2 %, oxygen saturation decreased after induction in the patients receiving methohexitone and thiopentone. For the infusion rates of 300 ml h^{-1}, 600 ml h^{-1} and 1200 ml h^{-1}, the percentage decreases in saturation in the patients receiving thiopentone were 3.1 %, 5.7 % and 6.9 % and in those receiving methohexitone were 6.5 %, 8.3 % and 2.9 %, respectively. At 2 min all these patients had oxygen saturations which had recovered to baseline values or greater, and these were maintained throughout the study. The etomidate group did not show this pattern and patients maintained their oxygen saturation after induction and later. There was no significant difference in oxygen saturation between infusion rates. The power of this finding was 0.75 using a postulated difference of oxygen saturation of 3 %.

Patients receiving thiopentone 1200 ml h^{-1} and 600 ml h^{-1} had an increase in heart rate from a baseline of 74 (SD 12.76) beat min^{-1} to 81 (14.28) beat min^{-1} and 76 (12.29) beat min^{-1}, respectively, immediately after induction. All the patients receiving methohexitone had increases in heart rate at the end of induction. From a baseline of 71 (8.1) beat min^{-1} the heart rate increased to 78.2 (8.2) beat min^{-1} in patients receiving 300 ml h^{-1}, 79.8 (9.0) beat min^{-1} in those receiving 600 ml h^{-1} and 74.2 (16.3) beat min^{-1} in those receiving 1200 ml h^{-1}. This was followed by a steady decline in heart rate of between 11% and 25% in the patients receiving thiopentone and of 2.7% and 6.2% in the patients receiving methohexitone. All patients receiving etomidate had only a steady decrease in heart rate of between 12.1% and 21.1% throughout the study period. None of these changes reached statistical significance between infusion rate groups. The power of this finding was 0.68 using a postulated difference in heart rate of 20%.

All patients had a steady decline in mean arterial pressure throughout the study. In the 300-ml h^{-1} group, the mean arterial pressure decreased by 30.1% in patients receiving thiopentone, 5% in those receiving methohexitone and 27.5% in those receiving etomidate. For the 600-ml h^{-1} group these values were 39.4%, 2.7% and 28.3%, respectively, and for the 1200-ml h^{-1} group, 23.2%, 6.2% and 28.3% (no statistical significance between induction rate groups). The power of this finding was 0.8 using a postulated difference in mean arterial pressure of 20%.

DISCUSSION

We have demonstrated that by reducing the rate of administration of thiopentone, methohexitone and etomidate, the induction dose given can be reduced to about 50% of the recommended dose. This is achieved at the expense of a longer induction time. These findings are similar to those described for propofol [1, 6].

In addition, we have measured plasma concentrations of these agents and found them to be reduced in the patients receiving slower infusion rates. The differences in serum concentrations of drug at 2 min were not significant because of a wide variation, probably as a result of incomplete mixing so soon after the start of induction. More complete mixing had occurred by 5 and 10 min, reducing the variation in drug concentration within infusion rate groups. Thus significance was reached at both 5 and 10 min after induction for thiopentone, and at 10 min for methohexitone. Although statistical significance was not reached in the etomidate group, the results demonstrate a trend similar to observations after administration of barbiturates. The AUC values calculated using these results confirm the above findings.

When a drug is administered until its action is observed to have taken effect, the amount required to induce anaesthesia depends on several factors: the free concentration of the drug in the plasma; the time it takes that drug to reach its target organ; the time it takes the drug to enter into the target organ in sufficient concentration; and the time it takes to exert its pharmacological action.

In patients given an i.v. agent at a fast infusion rate, a large amount of drug is given before it is able to reach the target organ. Thus the most important factor determining the dose given is the amount of drug that can be given in the time it takes for the drug to reach the target organ (or the "arm–brain circulation time"). The delay in the drug entering the central nervous system and exerting its action (biophase delay) is short, as the concentration gradient between blood and brain is large because of the larger dose. Attempting to titrate a dose against response in patients in whom anaesthesia is induced by fast infusion leads to overshoot, and so to overdose. This explains the findings with the 1200-ml h^{-1} infusion rate—a rate which corresponds, with thiopentone, to giving 250 mg over 30 s.

In patients given an i.v. anaesthetic agent by a slow infusion, the concentration of the drug in blood, and therefore in the brain, takes time to build up to a value sufficient to act. This may last as long as several complete circulations. This delay, together with the slower rate of administration, has the effect that overshoot is reduced, the total dose given being closer to the minimum dose required to achieve induction.

It is likely that reduction of delivery of a drug to less than a particular rate results in redistribution and elimination of the agent becoming significant factors in determining the rate at which sufficient plasma concentrations are reached, and the overall dose required to achieve induction may even begin to increase.

In a study by McCollum and Dundee comparing the induction characteristics of four i.v. anaesthetic agents [7], none of the patients receiving etomidate was apnoeic, but 30% of the patients receiving thiopentone and 20% of patients receiving methohexitone were so. In our study, the incidence of apnoea and respiratory depression were less in those patients receiving etomidate than in those receiving a barbiturate. These differences between agents are reflected in the pattern of change in oxygen saturation on induction.

Thiopentone and methohexitone also appeared to behave differently from etomidate in their effects on the cardiovascular system. The barbiturates produced an initial increase in heart rate after induction, followed by a decrease with deepening anaesthesia, the heart rate decreasing steadily throughout with etomidate. This early increase in heart rate with thiopentone has already been described [8]. In our study, the mean arterial pressure decreased with all three agents, probably because of cardiovascular depression caused by the maintenance of anaesthesia with enflurane. Enflurane was used to maintain anaesthesia in order to allow continuing sampling of plasma concentrations of the induction agent. The fact that we have been unable to demonstrate a significant difference in heart rate or mean arterial pressure between induction rate groups is at variance with the study using propofol. This difference may be accounted for in part by propofol causing more haemodynamic changes than the other agents [9, 10].

The recommended dose of an induction agent is that dose required to produce its effect in one arm–brain circulation time; this represents a dose greater than that needed to achieve sleep. Inducing anaesthesia in patients gradually may not eliminate the incidence of apnoea and hypotension, but perhaps we should re-assess the concept that an i.v. induction agent should be effective in a time approaching that taken by the blood to circulate from the arm to the brain.

REFERENCES

1. Peacock JE, Lewis RP, Reilly CS, Nimmo WS. The effect of different infusion rates of propofol for induction of anaesthesia in elderly patients. *British Journal of Anaesthesia* 1990; **65**: 346–352.
2. Toner W, Howard PJ, Dundee JW, McIlroy PDA. Estimation of plasma thiopentone. *Anaesthesia* 1979; **34**: 657–660.
3. Anderson LW, Qvist T, Hertz J, Morgensen F. Concentrations of thiopentone in mature breast milk and colostrum following an induction dose. *Acta Anaesthesiologica Scandinavica* 1987; **31**: 30–32.
4. Forbes RB, Murray DJ, Dillman JB, Dull DL. Pharmakinetics of two per cent rectal methohexitone in children. *Canadian Journal of Anaesthesia* 1989; **36**: 160–164.
5. DeBoer AG, Smeekens JB, Breimer DD. Assay of etomidate in plasma by capillary gas chromatography with nitrogen-selective detection. *Journal of Chromatography* 1979; **162**: 591–595.
6. Stokes DN, Hutton P. Rate-dependent induction phenomena with propofol: implications for relative potency of intravenous anaesthetics. *Anesthesia and Analgesia* 1991; **72**: 578–583.
7. McCollum JSC, Dundee JW. Comparison of induction characteristics of four intravenous anaesthetic agents. *Anaesthesia* 1986; **41**: 995–1000.
8. Seltzer JL, Gerson JI, Allen FB. Comparison of the cardiovascular effects of bolus *v.* incremental administration of thiopentone. *British Journal of Anaesthesia* 1980; **52**: 527–529.
9. Grounds RM, Twigley AJ, Carli F, Whitwam JG, Morgan M. The haemodynamic effects of intravenous induction. *Anaesthesia* 1985; **40**: 735–740.
10. Rolly G, Versichelen L. Comparison of propofol and thiopentone for induction of anaesthesia in premedicated patients. *Anaesthesia* 1985; **40**: 945–948.

British Journal of Anaesthesia 1993; 70: 428–433

HAEMODYNAMIC CHANGES PRODUCED BY INHALATION ANAESTHETICS IN THE PRESENCE OF PHOSPHODIESTERASE INHIBITION

G. MOLTER, R. LARSEN, U. PETERS, U. BAUCH AND R. SEFRIN

SUMMARY

We have investigated the circulatory effects of halothane and isoflurane in the presence of the phosphodiesterase inhibitor, enoximone, in 20 patients, ASA class III, aged 40–70 yr, undergoing coronary artery bypass grafting. After induction of anaesthesia (midazolam, fentanyl, etomidate and pancuronium) all patients received enoximone 0.5 mg kg^{-1}, followed, 10 min later, by either halothane 1 MAC (group I; n = 10) or isoflurane 1 MAC (group II; n = 10). Haemodynamic variables were measured and blood samples (arterial and mixed venous) were obtained before (control, t_0), 5 (t_1) and 10 (t_2) min after the injection of enoximone and immediately (t_3) and 5 (t_4) min after steady state conditions with halothane or isoflurane, as verified by the end-expiratory concentration. Heart rate, mean arterial pressure (MAP), mean pulmonary artery pressure, pulmonary capillary wedge pressure and right atrial pressure were recorded. Cardiac (CI) and stroke volume indices, systemic (SVR) and pulmonary vascular resistance, oxygen availability ($\dot{Q}O_2$), oxygen consumption and oxygen extraction rate were calculated using standard formulae. MAP decreased significantly in both groups after bolus injection of enoximone (group I: 11%; group II: 7%). Under steady state conditions with the volatile anaesthetics, a further significant decrease in MAP was observed (group I: 12%; group II: 12%). Enoximone produced a significant increase in CI (group I: 25%; group II: 27% compared with control). After administration of isoflurane, CI remained essentially unchanged, while halothane decreased CI significantly by 20%. In both groups, SVR decreased significantly after administration of enoximone (group I: 26%; group II: 24%). After isoflurane, there was a further significant decrease in SVR of 10%, whereas there was no change with halothane. After bolus injection of enoximone, $\dot{Q}O_2$ increased significantly (group I: 30%; group II: 23%). After halothane, $\dot{Q}O_2$ decreased significantly (20%), while with isoflurane there was no change. Oxygen extraction decreased significantly with enoximone (group I: 10%; group II: 15%); with halothane, it returned to control values, but it remained almost unchanged with isoflurane. (Br. J. Anaesth. 1993; **70**: 428–433)

KEY WORDS

Anaesthetics volatile: halothane, isoflurane. Pharmacology: enoximone.

In isolated heart muscle, equianaesthetic concentrations of halothane and isoflurane have similar negative inotropic effects. However, with enhanced active tension mediated by potentiating patterns of electrical stimulation, isoflurane has less negative inotropic action than halothane [1, 2]. It might be of greater clinical relevance if volatile anaesthetics have comparable depressant effects on a myocardium exposed to the positive inotropic action of cardiotonic agents. In order to examine this question, we have investigated the haemodynamic responses to halothane and isoflurane in the presence of enoximone.

PATIENTS AND METHODS

The study was approved by the local Human Subjects Medical Ethics Committee and patients' informed written consent was obtained. We studied 20 patients, ASA class III, aged 40–70 yr, undergoing coronary artery bypass grafting. All patients were receiving nitrates (isosorbide dinitrate) and calcium channel blockers (nifedipine) before operation. Patients with congestive heart failure (NYHA classification II–IV), an ejection fraction of less than 45%, renal failure (serum creatinine > 100 µmol litre^{-1}), medication with digitalis glycosides or beta-adrenergic receptor antagonists, or thrombocytopenia of platelets < 80000 µl^{-1} were excluded from the studies. The patients were allocated randomly to two groups (10 in each) according to a computerized allocating schedule.

Patients were premedicated with flunitrazepam 2 mg orally 1 h before arrival in the operating theatre. At the same time, the patient's scheduled oral medication with nitrates and calcium channel blockers was administered. Cutaneous electrodes were positioned for continuous electrocardiographic recording of leads II and V and continuous ST segment analysis (Sirecust 906, Siemens Inc.,

---

G. MOLTER, M.D.; R. LARSEN, M.D.; U. PETERS, M.D.; U. BAUCH, M.D.; R. SEFRIN, M.D.; Department of Anaesthesiology and Intensive Care, University of Saarland, D-6650 Homburg/Saar, Germany. Accepted for Publication: October 26, 1992.

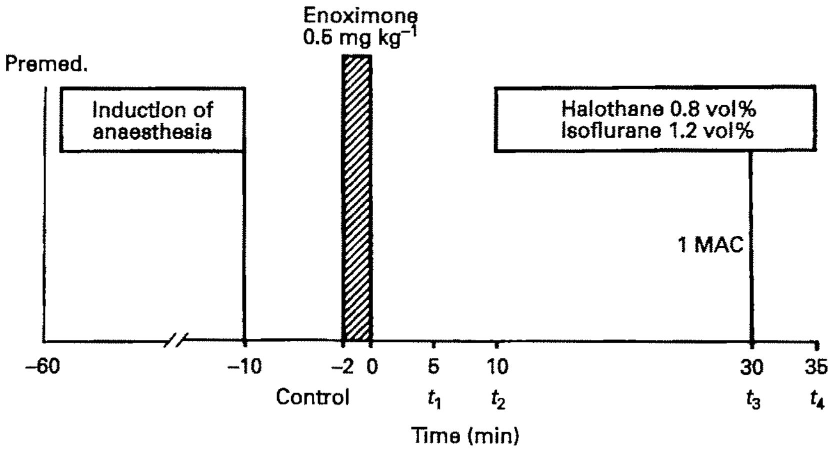


FIG. 1. Study design. After induction of anaesthesia every patient received enoximone 0.5 mg kg^{-1} i.v. within 2 min. Ten minutes after termination of that injection, patients received 1 MAC of either halothane (group I, $n = 10$) or isoflurane (group II, $n = 10$). Haemodynamic measurements were performed and blood samples were drawn before the injection of enoximone (control (t_0)) and 5 (t_1) and 10 (t_2) min after the bolus application of enoximone and immediately (t_3) and 5 (t_4) min after steady-state conditions with the volatile anaesthetics had established.

Danvers, MA, U.S.A.). Myocardial ischaemia was defined as a decrease in the ST level of more than 0.2 mV. After insertion of a venous cannula into a forearm vein and a 20-gauge Teflon cannula into the radial artery of the non-dominant arm, anaesthesia was induced with midazolam 1–2 mg, fentanyl 7–10 µg kg^{-1}, etomidate 0.2–0.3 mg kg^{-1} and pancuronium 0.1 mg kg^{-1}. The lungs were ventilated to normocapnia ($F\text{I}_{\text{O}_2}$ 1.0) (Sulla 808 V, Drägerwerk AG, Lübeck, FRG). A balloon-tipped thermodilution catheter was positioned in the pulmonary artery via the right internal jugular vein (7.5-French gauge pulmonary artery catheter, Baxter Lab., FRG). Catheter placement was determined by pressure tracing and confirmed by radioscopy. The catheters were connected to pressure transducers (Medex, Haslington, England) interfaced with a multichannel monitor and recorder (sirecust 906, siredoc 220, Siemens Inc. Danvers, MA, U.S.A.) for continuous monitoring of systemic arterial, pulmonary arterial and central venous pressure. Throughout the investigation period, crystalloid solution 10–15 ml kg^{-1} was administered.

Study design (fig. 1)

Ten minutes after induction of anaesthesia, each patient received enoximone 0.5 mg kg^{-1} within 2 min. Ten minutes later, 1 MAC (end-expiratory in oxygen) of either halothane (group I) or isoflurane (group II) was administered. Haemodynamic and oxygenation values (blood–gas analysis) (Stat profile 5, Nova biomedical, Waltham, MA, U.S.A.) were measured before injection of enoximone (control, t_0) and 5 (t_1) and 10 (t_2) min after the bolus administration of enoximone and immediately (t_3) and 5 (t_4) min after steady-state conditions with the volatile anaesthetics were established, as verified by the end-expiratory concentrations of halothane and isoflurane (Capnomac, Hoyer AG, Bremen, FRG).

Measured variables

The following haemodynamic variables were recorded: heart rate (HR), mean arterial pressure (MAP), right atrial pressure (RAP), mean pulmonary artery pressure (MPAP), pulmonary capillary wedge pressure (PCWP), cardiac output (CO).

Calculated variables

Systemic vascular resistance (SVR), pulmonary vascular resistance (PVR), cardiac index (CI), stroke volume index (SVI), oxygen availability ($\dot{Q}\text{O}_2$), oxygen consumption ($\dot{V}\text{O}_2$) and oxygen extraction rate ($\dot{V}\text{O}_2/\dot{Q}\text{O}_2$) were calculated by means of commonly used formulae:

SVR = (mean arterial pressure (MAP) —right atrial pressure (RAP)) × 80/cardiac output (CO)
PVR = (mean pulmonary artery pressure (MPAP) —left atrial pressure (LAP)) × 80/cardiac output (CO)
CI = cardiac output (CO)/body surface area (BSA)
SVI = stroke volume (SV)/body surface area (BSA)
$\dot{Q}\text{O}_2$ = cardiac output (CO) × arterial oxygen content ($C\text{a}_{\text{O}_2}$)
$\dot{V}\text{O}_2$ = cardiac output (CO) × arterio–mixed venous oxygen difference ($P\text{a}_{\text{O}_2}$–$P\bar{\text{v}}_{\text{O}_2}$)

Statistics

Mean values were calculated and within-group statistical analysis was performed using Friedman's test followed by a Wilcoxon–Wilcox test. In order to evaluate difference between groups, a Mann–Whitney *U* test was conducted. The 0.05 level of significance was used for all statistical tests. All values were expressed as mean (SD).

RESULTS

There were no statistically significant differences between the two groups in patient characteristics (table I).

MAP decreased significantly in both groups after bolus injection of enoximone (group I: 11%; group II: 7%) compared with control values. A further marked and significant decrease in MAP was

TABLE I. *Characteristics of the patients receiving enoximone 0.5 mg kg^{-1} followed by the application of 1 MAC of either halothane or isoflurane (mean (range or* SD*)). Group I: enoximone followed by halothane* (n = *10)); group II enoximone followed by isoflurane* (n = *10)). BSA = body surface area*

	Group I	Group II
Age (yr)	61.3 (40–70)	63.2 (43–68)
Weight (kg)	72.4 (6.8)	73.9 (6.8)
Height (cm)	170 (7)	167 (8)
BSA (m^2)	1.84 (0.11)	1.83 (0.13)

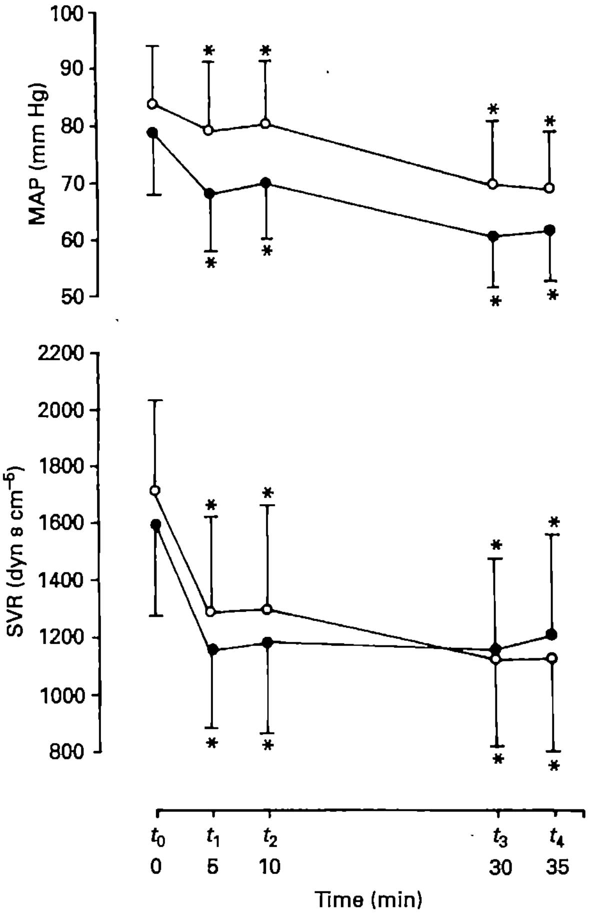


FIG. 2. Mean arterial pressure (MAP) and systemic vascular resistance (SVR) after bolus injection of enoximone 0.5 mg kg^{-1} (t_1, t_2) followed by the application of 1 MAC (steady state = t_3, t_4) of either halothane ($n = 10$) or isoflurane ($n = 10$) (mean, SD). ● = Enoximone followed by halothane; ○ = enoximone followed by isoflurane. *$P < 0.05$ compared with control.

observed with halothane (12%) and isoflurane (12%), respectively, in comparison with the values obtained with enoximone (fig. 2).

In both groups, SVR decreased significantly after administration of enoximone (26%, 24%) compared with control values. In the isoflurane group, there was a further moderate but significant decrease in SVR (10%) compared with values obtained with enoximone, whereas with halothane there was no further change (fig. 2).

Enoximone produced a significant increase in CI in both groups (25%, 27%) compared with the original control values. With isoflurane, CI remained essentially unchanged, while halothane decreased CI significantly by 20%, compared with the values after enoximone (fig. 3).

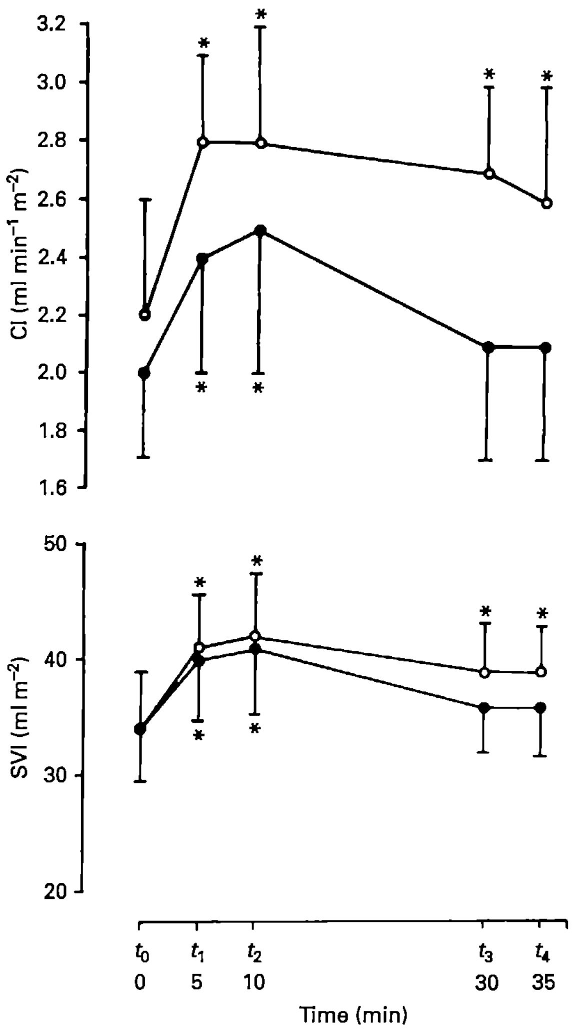


FIG. 3. Cardiac index (CI) and stroke volume index (SVI) after bolus injection of enoximone 0.5 mg kg^{-1} (t_1, t_2) followed by the application of 1 MAC (steady state = t_3, t_4) of either halothane ($n = 10$) or isoflurane ($n = 10$) (mean, SD). ● = Enoximone followed by halothane; ○ = enoximone followed by isoflurane. *$P < 0.05$ compared with control.

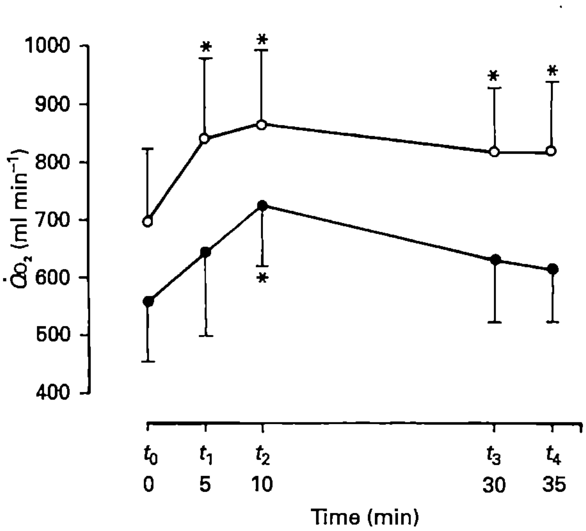


FIG. 4. Oxygen availability ($\dot{Q}o_2$) after bolus injection of enoximone 0.5 mg kg^{-1} (t_1, t_2) followed by the application of 1 MAC (steady state = t_3, t_4) of either halothane ($n = 10$) or isoflurane ($n = 10$) (mean, SD). ● = Enoximone followed by halothane; ○ = enoximone followed by isoflurane. *$P < 0.05$ compared with control.

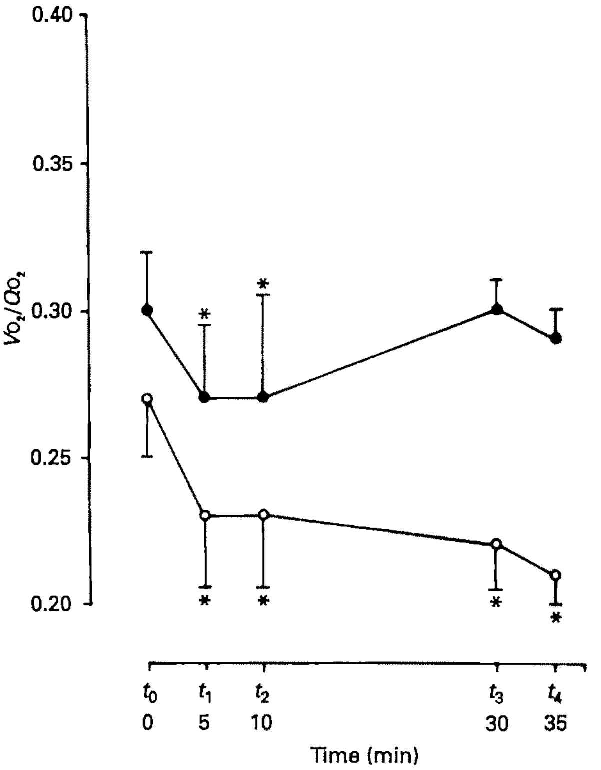


FIG. 5. Oxygen extraction rate $\dot{V}o_2/\dot{Q}o_2$ after bolus injection of enoximone 0.5 mg kg^{-1} (t_1, t_2) followed by the application of 1 MAC (steady state = t_3, t_4) of either halothane ($n = 10$) or isoflurane ($n = 10$) (mean, SD). ● = Enoximone followed by halothane; ○ = enoximone followed by isoflurane. *$P < 0.05$ compared with control.

A similar pattern was observed with SVI. After injection of enoximone, SVI increased significantly, by 21% in group I and 24% in group II, compared with control. With halothane there was a significant decrease in SVI (15%) in comparison with the values obtained with enoximone, whereas isoflurane had almost no effect (fig. 3).

$\dot{Q}o_2$ increased significantly after i.v. injection of enoximone in both groups (group I: 30%; group II: 23%) compared with control, decreased significantly after halothane (20%) compared with values obtained with enoximone, but remained essentially unchanged with isoflurane (fig. 4).

With enoximone, $\dot{V}o_2/\dot{Q}o_2$ decreased significantly in both groups (group I: 10%; group II: 15%) in comparison with control values. With halothane, it increased significantly (10%) compared with the values after enoximone and returned to control, whereas with isoflurane there was no change (fig. 5).

There were no statistically significant changes within groups or between groups in heart rate, filling pressures, pulmonary haemodynamics and oxygen consumption (table II).

With continuous ECG analysis, there were no changes in ST segments of more than 0.1 mV.

DISCUSSION

The cardiotonic effect of any drug results ultimately from an increase in the concentration of intracellular free calcium available to interact with the contractile proteins, an increased sensitivity of the myofilaments to calcium, or both [3]. Phosphodiesterase (PDE) inhibiting agents increase the amount of intracellular cyclic adenosine monophosphate (cAMP), thereby enhancing protein phosphorylation and subsequently increasing calcium availability at the myofilaments.

Enoximone, a specific PDE inhibitor, interacts with the PDE isoenzyme III, which is present in myocardial and vascular smooth muscles. This interaction leads to an increase in myocardial contractile performance and to a decrease in vascular smooth muscle tone—two effects which are demonstrated in our study: after injection of enoximone, there was an increase in CI and SVI, whereas SVR decreased markedly. The increases in CI and SVI were most probably caused by the positive inotropic effect of enoximone, resulting mainly from inhibition of cardiac PDE III, leading to an increase in myocardial cAMP content. However, some drugs with PDE inhibiting activity have a direct effect on myofibrils, by sensitizing them to Ca^{2+} and thus the myocardial force of contraction is increased independently of changing calcium concentrations [3]. This effect has been observed with other agents with PDE inhibitor actions (pimobendan and imidazodan), but it is unlikely to occur with the selective PDE agents currently available for clinical use [4, 5]. It has been reported previously that PDE inhibitors improve haemodynamic state in patients with acute heart failure after myocardial infarction [6, 7] and with low output syndrome after cardiac or general surgery [8–10].

In patients after coronary revascularization, the inotropic response of PDE inhibitors has been shown to be comparable to that of dobutamine, but the vasodilator activity of dobutamine may be greater [11, 12]. It has been proved, by *in vitro* studies [13] and after direct intracoronary injections [14], that PDE inhibitors used clinically possess positive inotropic activity.

Marked vasodilatation and the resulting decline in SVR after injection of enoximone, observed in the patients in our study, may be a result of increased cAMP content in vascular smooth muscle cells. Increased concentrations of cAMP lead to phosphorylation of the enzyme myosin light-chain kinase, thereby dephosphorylating myosin light chains, resulting in vasodilatation [3]. Smooth muscle relaxation is also mediated by cyclic guanosine monophosphate (cGMP), via cGMP-dependent protein kinases [15]. Cyclic GMP-mediated vasodilatation may have contributed to the marked decrease in SVR in our patients, as PDE III isoenzymes, although proved to be "high affinity cAMP PDE", also hydrolyse cGMP [16]. In isolated limb studies in resting patients with heart failure, SVR was mainly reduced in skeletal muscles [17–20].

In the present study, enoximone produced a marked decrease in MAP in all patients. This agrees with the findings of other investigators who showed that PDE inhibitors may lead to profound vasodilatation and hypotension [21]. Furthermore, it has been stressed that the pharmacodynamic effects of amrinone suggest predominant vasodilatation,

TABLE II. *Haemodynamic variables and oxygenation values after bolus injection of enoximone 0.5 mg kg^{-1} followed by the application of 1 MAC of either halothane or isoflurane (mean (SD)).* t_0 = *Control;* t_1, t_2 = *5 and 10 min after bolus injection of enoximone;* t_3, t_4 = *immediately and 5 min after steady-state conditions (1 MAC) with the volatile anaesthetics. Group I: enoximone followed by halothane* (n = *10*)*; group II = enoximone followed by isoflurane* (n = *10*)

	Control	Enoximone 0.5 mg kg^{-1}		Halothane or isoflurane 1 MAC	
	t_0	t_1	t_2	t_3	t_4
HR (beat min^{-1})					
Group I	60.5 (8.8)	64.9 (8.3)	64.0 (8.7)	59.5 (8.5)	58.9 (8.3)
Group II	66.0 (9.9)	69.1 (9.2)	68.7 (9.3)	69.8 (9.4)	69.2 (9.6)
MPAP (mm Hg)					
Group I	14.2 (3.0)	13.6 (3.0)	14.1 (2.5)	12.8 (2.7)	13.1 (2.9)
Group II	13.8 (3.7)	13.6 (3.7)	13.3 (3.1)	12.8 (1.7)	14.3 (4.4)
PCWP (mm Hg)					
Group I	8.7 (1.3)	8.2 (1.6)	8.1 (1.7)	7.7 (1.4)	7.9 (1.3)
Group II	8.6 (1.4)	8.0 (1.3)	8.8 (1.4)	7.4 (0.9)	7.4 (1.0)
PVR (dyn s cm^{-5})					
Group I	115 (29)	98 (18)	110 (21)	107 (22)	111 (21)
Group II	117 (30)	101 (27)	105 (27)	95 (18)	116 (24)
RAP (mm Hg)					
Group I	6.1 (0.9)	5.9 (1.0)	5.2 (1.0)	5.3 (0.8)	5.4 (0.8)
Group II	6.0 (0.9)	6.2 (0.9)	6.0 (0.9)	5.4 (0.9)	5.8 (0.9)
Pa_{O_2} (kPa)					
Group I	40.5 (9.5)	37.2 (9.6)	43.5 (11.2)	44.5 (8.5)	40 (12.8)
Group II	51.3 (10.5)	49.1 (11.6)	49.6 (11.5)	51.2 (12.1)	49.5 (12.4)
$P\bar{v}_{O_2}$ (kPa)					
Group I	4.7 (0.8)	4.7 (0.9)	5.3 (0.8)	5.0 (0.9)	5.0 (0.9)
Group II	5.4 (0.6)	5.9 (0.8)	5.9 (0.8)	5.9 (0.6)	6.1 (1.1)
$\dot{V}O_2$ (ml min^{-1})					
Group I	165 (35)	171 (37)	191 (39)	182 (44)	175 (36)
Group II	188 (46)	187 (45)	187 (41)	172 (43)	168 (33)

whereas the positive inotropic effect was less important [22]. It is questionable if this is true for enoximone. It is assumed that the relative contributions of the vasodilator and inotropic action of PDE inhibitors depend on the patient in specific clinical circumstances [3].

Enoximone has been shown to shorten atrial and atrioventricular node refractoriness and ventricular refraction [23]. These features enable enoximone to produce increases in heart rate and atrial or ventricular arrhythmias. In the present study, there was no evidence of increased atrioventricular node conduction or atrial or ventricular refraction shortening, as heart rate remained unchanged and arrhythmias did not occur. Other investigators showed that milrinone [24] and amrinone [25] are associated with either no change or an increase in ventricular arrythmias.

The reduction of mean arterial pressure in our patients may have compromised coronary artery perfusion. It has been shown that there is a reduction of regional coronary vascular resistance with PDE inhibitors [26, 27], resulting in increased myocardial perfusion. Coronary vasodilatation may induce intracoronary steal, but there has been no clinical evidence of myocardial ischaemia with PDE inhibitors. In patients with proven coronary artery stenosis undergoing ventricular pacing studies, i.v. enoximone has been shown to increase the anginal threshold while left ventricular stroke work index was maintained [28]. Furthermore, PDE inhibitors have been shown to increase cardiac index without compromising the myocardial supply to demand ratio [29]. In our patients, there were no changes in ST levels indicative of myocardial ischaemia, although this does not exclude imbalance in myocardial oxygen supply to demand.

The observations made after administration of the volatile anaesthetics largely confirm the well known cardiovascular effects of halothane and isoflurane. In summary, we found that heart rate remained unchanged with halothane; MAP was reduced by halothane and isoflurane; SVR decreased with isoflurane, but was not affected by halothane; SVI declined with halothane; and CI and $\dot{Q}O_2$ decreased and $\dot{V}O_2/\dot{Q}O_2$ increased with halothane.

Some results were not consistent with previous knowledge of the effects of volatile agents. After i.v. enoximone, heart rate remained unchanged with isoflurane; SVI essentially remained unchanged with isoflurane; and CI, $\dot{Q}O_2$ and $\dot{V}O_2/\dot{Q}O_2$ were almost not affected with isoflurane.

Our data indicate that, under the influence of enoximone, the mechanisms of action responsible for circulatory depression differ with halothane and isoflurane. While isoflurane appears to cause a reduction in MAP primarily by vasodilatation, halothane acted primarily by myocardial depression.

In conclusion, our results suggest that, in contrast with halothane, isoflurane enhances the vasodilator action of enoximone, and that halothane attenuates the positive inotropic action of enoximone to a far greater extent than isoflurane in patients with coronary artery disease.

ACKNOWLEDGEMENTS

We gratefully acknowledge the work of three members of our nurse staff, Christa Hölcker, Michael Trautmann and Jürgen Salamon who gave great support in performing this study.

REFERENCES

1. Komai H, Rusy BF. Negative inotropic effects of isoflurane and halothane in rabbit papillary muscles. *Anesthesia and Analgesia* 1987; **66**: 29–33.
2. Lynch C. Effects of halothane and isoflurane on isolated human ventricular myocardium. *Anesthesiology* 1988; **68**: 429–432.
3. Skoyles JR, Sherry KM. Pharmacology, mechanisms of action and uses of selective phosphodiesterase inhibitors. *British Journal of Anaesthesia* 1992; **68**: 293–302.
4. van der Leyen H. Phosphodiesterase inhibition by new cardiotonic agents: mechanism of action and possible clinical relevance in therapy of congestive heart failure. *Klinische Wochenschrift* 1989; **67**: 605–615.
5. Reugg JC. Effects of new inotropic agents on Ca^{++} sensitivity of contractile proteins. *Circulation* 1986; 74 (Suppl. III): 78–84.
6. Renard M, Dereppe H, Henuzet C, Stevens E, Bernard R. Effects of enoximone in patients with heart failure after myocardial infarction. *British Journal of Clinical Practice* 1988; 42 (Suppl. 64): 37–40.
7. Taylor S, Verma S, Hussain M. Intravenous amrinone in left ventricular failure complicated by acute myocardial infarction. *American Journal of Cardiology* 1985; 56: 2B–32B.
8. Goenen M, Pedermonte O, Baele P. Amrinone in the management of low output after open heart surgery. *American Journal of Cardiology* 1985; 56: 33–38.
9. Gonzalez MM, Desager J-P, Jacquemart J-L, Chenu P, Muller T, Installe E. Efficacy of enoximone in the management of refractory low output states following cardiac surgery. *Journal of Cardiothoracic Anaesthesia* 1988; 2: 409–418.
10. Wright EM, Sherry KM. Clinical and haemodynamic effects of milrinone in the treatment of low cardiac output following cardiac surgery. *British Journal of Anaesthesia* 1991; **67**: 585–590.
11. Gilbe CE, Priddy R, Keogh B, Morgan C. A study of the postoperative effects of enoximone and dobutamine in patients with impaired left ventricular function. *Journal of Cardiothoracic Anaesthesia* 1990; 4 (Suppl. 30): 84.
12. Lancon JP, Rosay H, Fontaine P, Obidia JF, Merle F, Bock F, Aillard B. Enoximone versus dobutamine in low output after cardiopulmonary bypass. *Journal of Cardiothoracic Anaesthesia* 1990; 4 (Suppl. 3): 83.
13. Alousi AA, Farah AE. Amrinone, a new oral and parenteral cardiotonic agent. *Trends in Pharmacological Sciences* 1980; 1: 143–146.
14. Ludmer PL, Wright RF, Arnold JMO, Ganz P, Braunwald E, Colucci WS. Separation of the direct myocardial and vasodilator actions of milrinone administered by an intracoronary infusion technique. *Circulation* 1986; 73: 130–137.
15. Lincoln TM. Cyclic GMP and mechanisms of vasodilation. *Pharmacology and Therapeutics* 1989; 41: 479–502.
16. Nicholson CD, Challis RAJ, Shahid M. Differential modulation of tissue function and therapeutic potential of selective inhibitors of cyclic nucleotide phosphodiesterase isoenzymes. *Trends in Pharmacological Sciences* 1991; 12: 19–27.
17. Cody RJ, Muller FB, Kubo SH, Rutman H, Leonard D. Identification of the direct vasodilating effect of milrinone with an isolated limb preparation in patients with congestive heart failure. *Circulation* 1986 73: 124–129.
18. Colucci WS. Do the bipyridines exert a positive effect in patients with congestive heart failure? In: Braunwald E, Julian D, eds. *The Acute Therapy of Heart Failure*. London: Royal Society of Medicine, 1991; 11–17.
19. Lejemtel TH, Maskin CS, Lucido D, Chadwicc BJ. Failure to augment maximal limb blood flow in response to one leg or two leg exercise in patients with severe heart failure. *Circulation* 1986; 74: 245–251.
20. Lejemtel TH, Scortichini D, Levitt B, Sonnenblick EH. Effects of phosphodiesterase inhibition on skeletal muscle vasculature. *American Journal of Cardiology* 1989; **63**: 27A–30A.
21. White DA, Latimer RD, Oduro A. Management of low cardiac output syndrome after cardiac surgery using enoximone. *Anaesthesia* 1990; 45: 386–389.
22. Wilmshurst PT. Phosphodiesterase inhibitors. *Current Opinion in Anaesthesiology* 1989; 2: 83–87.
23. Miles WM, Heger JJ, Minardo JD, Prystowsky EN, Zipes DP. Electrophysiologic and hemodynamic effects of intravenous enoximone. *Circulation* 1986; 74 (Suppl. II): 11–38.
24. Goldstein RA, Geraci SA, Gray EL, Rinkenberger RL, Dougherty AH, Nacarelli GV. Electrophysiologic effects of milrinone in patients with congestive heart failure. *American Journal of Cardiology* 1986; 57L: 624–628.
25. Naccarelli GV, Gray EL, Dougherty AH, Hanna JE, Goldstein RA. Amrinone; acute electrophysiologic and hemodynamic effects in patients with congestive heart failure. *American Journal of Cardiology* 1984; 54: 600–604.
26. Amin DK, Shah PK, Hulse S, Shellock FG, Swan HJ. Myocardial metabolic and hemodynamic effects of intravenous MDL-17043, a new cardiotonic drug in patients with severe heart failure. *American Heart Journal* 1984; **108**: 1285–1292.
27. Monrad ES, Baim DS, Smith HS, Lanoue A, Braunwald E, Grossmann W. Effects of milrinone on coronary hemodynamics and myocardial energetics in patients with congestive heart failure. *Circulation* 1985; 71: 972–979.
28. Thormann J, Kremer P, Mitrovic V, Neuzner J, Bahavar H, Schleppner M. Effects of enoximone in coronary artery disease: increased pump function, improved ventricular wall motion and abolition of pacing induced myocardial ischemia. *Journal of Applied Cardiology* 1989; 4: 152–167.
29. Benotti JR, Grossmann W, Braunwald E, Carabello BA. Effects of amrinone on myocardial energy metabolism and hemodynamics in patients with severe congestive cardiac failure due to coronary heart disease. *Circulation* 1980; **62**: 28–34.

British Journal of Anaesthesia 1993; 70: 434–439

REVIEW ARTICLE

THE VALUE OF PRE-EMPTIVE ANALGESIA IN THE TREATMENT OF POSTOPERATIVE PAIN

J. B. DAHL AND H. KEHLET

Our knowledge and understanding of the physiology of acute pain has improved in recent years. Most of this new information has been gathered from basic science and experimental studies. The recent papers by Wall [40] and Woolf [41] have stimulated much discussion on the potential clinical implications of this knowledge for the management of acute postoperative pain, and the concept of "pre-emptive analgesia" has gained widespread acceptance. This paper is a critical analysis of clinical studies on the effects of pre-emptive analgesia on acute postoperative pain.

BACKGROUND

Tissue injury results in disruption of the normal specialization of the CNS, with alterations in the processing of afferent stimuli [41, 42]. Experimental studies have demonstrated that peripheral injury may result in expansion of receptive fields and decrease in the threshold of dorsal horn neurones [13, 14, 41, 42]. This facilitation may be prolonged, depending on the stimulus and the type of afferents activated [41, 42]. Consequently, innocuous inputs may generate pain (allodynia), with increased pain to suprathreshold stimulation (hyperalgesia) and development of spontaneous pain [41, 42]. The neurophysiological and molecular mechanisms of these changes may involve an increase in synaptic efficacy of excitatory inputs or a decrease in inhibitory inputs [13, 42] mediated by wind-up [31], and neurokinin and N-methyl-D-aspartate (NMDA) receptor mechanisms [10, 14, 42]. Furthermore, changes in second messengers and gene expression may lead to prolonged functional changes in the nervous system [14].

In humans, cutaneous injury is followed by alterations in thermal and mechanical sensibility [19, 25, 26, 33]. "Primary hyperalgesia" refers to changes within the area of injury and "secondary hyperalgesia" to changes in the undamaged tissue surrounding the injury. Primary hyperalgesia is explained by sensitization of peripheral nociceptors [19, 25, 26, 33]. A recent series of elegant studies in humans and primates supported the suggestion that secondary hyperalgesia is caused by altered central processing of mechanoreceptive input from the periphery [2, 24, 25, 36, 38]. Based on these experimental and clinical studies, it has been proposed that surgical trauma in humans may lead to comparable alterations in sensory processing, resulting in amplification and prolongation of postoperative pain, and possibly persistent postsurgical pain [40–42].

To date, only four studies have investigated the effect of surgery on pain sensitivity in humans [7, 17, 18, 27]. Postoperative sensory thresholds were reported to be unaffected [17, 18] or increased [27], but in the latter study, only perception thresholds to electrical stimulation were investigated—not pain thresholds, which would have been more appropriate [27]. Recently, increased sensitivity and pain to noxious electrical stimulation in the A-β range were observed in patients after gynaecological surgery [7]. Furthermore, the threshold of the nociceptive flexion reflex was decreased in the early (48 h) postoperative phase [7]. These observations of allodynia and hyperalgesia in postoperative patients may be a result of postoperative sensitization of central neurones. However, no conclusion on the relative contribution of central sensitization to postoperative pain can be derived from these studies. Thus data demonstrating neuronal plasticity in postoperative patients are limited and the relative contributions of central sensitization to the intensity and duration of acute pain in humans have not been identified. No information is available on the degree or duration of noxious inputs required to induce central changes, or the question if postoperative pain itself may lead to alterations in dorsal horn excitability, independent of the afferent barrage during surgery. Finally, it is not known if the intensity and maintenance of postoperative pain is more dependent on central hyperexcitability than continuous afferent barrage from the wound.

"PRE-EMPTIVE ANALGESIA"

In experimental studies, acute pain behaviour or hyperexcitability of dorsal horn neurones may be eliminated or reduced if the afferent barrage is prevented from reaching the CNS by *pre*-injury neural block with local anaesthetics [4, 5, 44] or if

(Br. J. Anaesth. 1993; **70**: 434–439)

KEY WORDS

Analgesia: pre-emptive. Pain: postoperative.

J. B. DAHL, M.D. (Department of Anaesthesia); H. KEHLET, M.D., PH.D. (Department of Surgical Gastroenterology); Hvidovre University Hospital, DK-2650 Hvidovre, Denmark. Accepted for Publication: September 29, 1992.

TABLE I. *Summary and interpretation of studies used in the discussion on the potential clinical value of pre-emptive analgesia. Section I: Comparative studies of identical* pre- *and* post*operative neural block. Section II: Studies comparing* pre*operative neural block with no block. Section III: Studies of* pre*operative opioids compared with no or* post*operative opioids. Section IV: Studies with* pre- *plus* post*operative NSAID compared with* post*operative NSAID only. Section V: Other studies (see text). LA = Local anaesthesia; TENS = transcutaneous electrical nerve stimulation*

Study	Type of analgesia in pre-emptive group	Type of surgery	Results: does *pre-emptive* analgesia improve post-operative pain relief?
Section I			
[16]	Wound infiltration LA	Inguinal herniorrhaphy	Partially supportive
[12]	Ileo-inguinal block and wound infiltration LA	Inguinal herniorrhaphy	Not supportive
[8]	Extradural bupivacaine plus morphine	Colonic surgery	Not supportive
Section II			
[30]	Opioid premedication, peripheral LA blocks combination opioid premedication and LA	Various peripheral orthopaedic procedures	Interpretation hindered by methodological deficiencies
[39]	Wound infiltration LA	Inguinal herniorrhaphy	May be supportive, but other mechanisms than modulation of central hyperexcitability may be effective
[3]	Ileo-inguinal block + spinal anaesthesia	Inguinal herniorrhaphy	May be supportive, but other mechanisms than modulation of central hyperexcitability may be effective
[20]	Wound infiltration LA	Tonsillectomy	May be supportive, but other mechanisms than modulation of central hyperexcitability may be effective
[32]	Subdiaphragmatic LA	Gynaecological laparoscopy	May be supportive, but other mechanisms than modulation of central hyperexcitability may be effective
[34]	Extradural LA + morphine + systemic indomethacin	Cholecystectomy	Not supportive
[Unpublished]	Extradural LA + morphine	Mini laparotomy–cholecystectomy	Not supportive
Section III			
[21]	Extradural morphine	Trans-sternal thymectomy	Not supportive
[23]	High-dose systemic alfentanil	Abdominal surgery	Not supportive
[22]	Premedication	Lumbar disc prolapse surgery	Interpretation hindered by methodological deficiencies
Section IV			
[15]	Pre- and postoperative flurbiprofen	Oral surgery	Interpretation hindered by methodological deficiencies
Section V			
[1]	Extradural bupivacaine or opioid or combination	Lower limb amputation	Interpretation somewhat hindered by methodological deficiencies. Patients with *pre*operative pain cannot be extrapolated to other surgical procedures
[37]	TENS and extradural bupivacaine	Caesarean section	Interpretation hindered by methodological deficiencies

the excitability of the CNS is suppressed with opioids *before* it receives a nociceptive input [11, 43]. Similar antinociceptive procedures were less effective when applied *post*-injury [5, 11, 43, 44], although one study showed spinal anaesthesia 5 min after the injury also to be effective [4]. Consequently, the importance of "timing" of analgesia has been suggested to be of potential major importance in the treatment of postoperative pain [40–42].

Clinical studies of pre- *and* post*operative neural block or wound infiltration with local anaesthetics* (table I, section I)

Only three studies have been published comparing the postoperative analgesic effect of an identical neural block administered before or after the surgical stimulus [8, 12, 16]. Two studies compared the effect of *pre*- and *post*operative local infiltration with lignocaine on pain after inguinal herniorrhaphy [12, 16]. In one study, there was no difference in pain scores, but the time to first request for additional analgesia (non-steroidal anti-inflammatory drug (NSAID)/opioid) was increased in patients with preoperative infiltration of the surgical area compared with a similar postoperative block [16]. However, pain was evaluated for only 6 h after operation [16]. In the other herniorrhaphy study, there was no significant difference in times to first request for morphine, total morphine requirements or pain scores at rest or during physical activity, between patients with an inguinal field block performed before compared with after surgery. Patients were followed up for 7 days after operation [12]. In the third study, patients undergoing colonic surgery received either an extradural dose of 9 ml of bupivacaine 7.5 mg ml^{-1} plus morphine 2 mg before or after surgery, followed by low-dose continuous extradural bupivacaine 0.25 mg ml^{-1} plus morphine 0.2 mg ml^{-1} at a rate of 4 ml h^{-1} for 72 h [8]. The results showed no significant differences in pain scores at rest or during mobilization, or in request for additional morphine [8].

Thus, from these few studies, there is no firm evidence that timing of analgesic treatment—that is, pre-emptive analgesia—has important effects on postoperative pain or requirements for additional analgesics. Obviously, more studies in other procedures and with different pre-emptive analgesia regimens are required, and studies are needed to evaluate the effect of such regimens on the occurrence of very late (chronic) postoperative pain.

Preoperative neural block or wound infiltration with local anaesthetics compared with no treatment or placebo (table I, section II)

In a non-randomized, retrospective study, McQuay, Carroll and Moore [30] investigated patients undergoing a variety of surgical procedures on the extremities and receiving either *pre*operative opioids or no premedication, a variety of local anaesthetic blocks, or both. The results showed that median time to first request for postoperative analgesia was prolonged significantly by opioid premedication, by a local anaesthetic block and by a combination of premedication and a local anaesthetic block, with increased analgesic efficacy in that order. However, this non-randomized study in badly defined analgesic techniques and patients did not address the question of the value of pre-emptive analgesia (that is, timing of analgesia *per se*) and the design of the study prevents interpretation in this context.

In a prospective, randomized study, preoperative incisional local anaesthetic combined with general anaesthesia in patients undergoing inguinal herniorrhaphy was compared with general anaesthesia alone and with spinal anaesthesia [39]. The study is outstanding, as pain at rest and mobilization, and wound tenderness were assessed by algometer. The study was well designed, with well defined postoperative additional analgesic treatment and only one surgeon, performing a well defined procedure. The results showed that *pre*operative incisional neural block provided superior and prolonged analgesia for 24 h and 48 h after operation, compared with general anaesthesia alone, while the spinal anaesthesia group had an intermediary analgesic response. The prolonged analgesic effects of incisional local anaesthetic obviously could be caused by reduction of central hyperexcitability, although this was not documented by the study, as a similar analgesic procedure applied after operation was not investigated. Another explanation for these positive findings could be reduction of the primary hyperalgesic response resulting from the well documented anti-inflammatory effects of local anaesthetics in *in vitro* and experimental studies [39].

In another study, *pre*operative spinal anaesthesia and percutaneous ileoinguinal nerve block were found to reduce postoperative pain for 48 h after herniorrhaphy compared with pain in patients operated under spinal anaesthesia only [3]. Pain was assessed only at rest and interpretation is somewhat hindered by a badly defined additional analgesic treatment with different drugs, although it was stated that the overall need for additional analgesics was reduced in the combined spinal–inguinal block group [3]. Again, this study may support the concept that *pre*operative neural block may reduce late *post*operative pain in small scale surgery, but a similar analgesic procedure applied after operation was not studied.

A study in 14 patients, aged 6–18 yr, undergoing tonsillectomy demonstrated that 0.25 % bupivacaine 3 ml/tonsil significantly reduced the constant pain score for 6 days compared with a saline control group. Pain on swallowing was also reduced significantly by the preoperative block for up to 10 days after operation [20]. Surgery was undertaken by the same surgeon and treatment blinded for the assessor of pain. Postoperative pain was treated with paracetamol, apparently with the same dosing regimen in both groups. Again, these very positive results may be explained by reduction of central hyperexcitability as in the study by Tverskoy and colleagues [39], but an effect mediated by reduction of primary hyperalgesia from the anti-inflammatory effects of bupivacaine cannot be excluded.

In a study in patients undergoing day-case laparoscopy, 80 patients were allocated randomly to initial subdiaphragmatic administration of 0.25 % bupivacaine 80 ml, 1 % lignocaine 80 ml with adrenaline, saline 80 ml or no peritoneal administration [32]. Pain scores at rest were reduced significantly in the local anaesthetic treatment groups compared with the non-treatment groups for up to 48 h after operation. Although no information was given on postoperative additional analgesics in this study, the results again may support the concept of pre-emptive analgesia and reduction in central hyperexcitability, although this was not proven, and an effect on peripheral nociceptors caused by anti-inflammatory effects cannot be excluded.

In two randomized, but not double-blind studies in patients undergoing classical cholecystectomy [34] or laparoscopic cholecystectomy [unpublished observations] (who recieved intensive *pre*operative extradural analgesia with 0.5 % or 0.75 % bupivacaine combined with *pre*operative extradural morphine followed by continuous extradural combined bupivacaine and opioid treatment), the initial extremely effective analgesia during rest, cough and mobilization did not result in prolonged pain relief during physical activity, when the initial block disappeared. These two studies document clearly that clinically relevant and very effective extradural analgesic regimens, even when administrated before operation, have no important effect on later postoperative pain during physical activity and therefore do not suggest that pre-emptive analgesia, even when combined with relatively prolonged postoperative analgesia, "prevents" or reduces late postoperative pain.

Pre-emptive anaesthesia with opioids (table I, section III)

In one randomized, placebo-controlled double-blind study in patients undergoing trans-sternal thymectomy, preoperative extradural morphine 7 mg compared with saline had no effect on postoperative pain scores at rest or on additional analgesic requirements beyond the initial 8-h postoperative period [21]. However, the study was small including only 19 patients. In another randomized, placebo-controlled study, a *pre*operative bolus of alfentanil 30 μg kg^{-1} followed by an intraoperative infusion of 40 μg kg^{-1} h^{-1} had no effect on *post*operative pain scores or requirement for additional opioids [23]. These two studies [21, 23], therefore, do not support experimental studies with minimal trauma [11, 43] to suggest that *pre*injury administration of opioids can reduce *post*operative pain.

Finally, a non-randomized study in patients undergoing lumbar disc prolapse surgery and receiving a variety of premedicant drugs, concluded that additional opioid premedication reduced time to first demand for a postoperative analgesic and the overall need for postoperative analgesia [22]. Because of major methodological deficiencies and differences in sex distribution and with the finding that women required more analgesics than men, this study is unable to make the conclusion that "it is confirmed that opiate premedication diminishes the sustained hyperexcitability of the central nervous system caused by intraoperative stimuli" [22].

Pre-emptive analgesia with NSAID (table I, section IV)

Only one study has examined combined *pre-* and *post*operative NSAID (flurbiprofen) compared with *post*operative flurbiprofen alone on postoperative analgesia after removal of the third molar [15]. The results suggested that the combination was more effective, which is not unexpected, as the total dose of NSAID was larger in the combined treatment group, and therefore the results cannot be taken as an argument for increased efficacy of pre-emptive analgesia compared with *post*injury treatment.

Other studies (table I, section V)

In the discussion on the potential clinical importance of pre-emptive analgesia, the studies by Bach, Noreng and Tjellden [1] and Smith and colleagues [37] have been used to support the hypothesis of a preoperative neural block reducing central hyperexcitability, postoperative pain and analgesic requirements [6, 40]. The former study [1] in 26 patients undergoing limb amputation allocated randomly to *pre-* and *intra*operative extradural block or *intra*operative block alone, assessed the occurrence of phantom limb pain for the subsequent 12 months. Only patients with preoperative pain were included, but pre- and postoperative pain scores in the two groups were not presented. There was no information on the extradural regimen, except that it was provided for 3 days by extradural morphine or 0.25% bupivacaine or a combination, aiming at freedom from pain, although this was not assessed or documented. The authors stated that patients who continued to have pain despite the *pre*operative extradural block were excluded from further investigation, but no information was given on the number of patients excluded. However, apparently no patient was excluded [M. Noring, personal communication]. Extradural analgesia was not given after operation in any group. The results showed a significant reduction in phantom limb pain 6 months after operation, with a non-significant similar trend 7 days and 1 yr after operation. The degree of phantom limb pain was not presented. Although very interesting, great care should be taken in the interpretation of this study, because of several inadequacies in its design, and the results cannot be extrapolated to patients undergoing elective surgery who have no preoperative pain. However, despite this criticism, the study has stimulated much constructive debate on pre-emptive analgesia and the potential impact of such treatment on the occurrence of *late* and *chronic*, postoperative pain. Obviously, further well designed studies are required to answer this important and clinically relevant question.

A study [37] quoted to support the efficacy of pre-emptive analgesia [6, 40] considered 18 women undergoing elective Caesarean delivery, nine patients receiving transcutaneous electrical nerve stimulation (TENS) and nine placebo stimulation. In addition, and confounding for the interpretation, some of the patients received extradural anaesthesia and some general anaesthesia; exact numbers receiving each were not given [37]. Exact pain data were not presented, but it was mentioned that a non-significant reduction in constant and movement-associated incisional pain was found in the TENS treated women in the extradural group, and that the placebo treated women had significantly less movement-associated pain when receiving extradural analgesia. Obviously, these results in small groups of patients, together with a combination of different analgesic treatments and without presentation of exact data, cannot be taken as an indication of extension of analgesic efficacy of a *pre*operative neural block into the *post*operative period.

COMMENTS AND CONCLUSIONS

Available data from the few studies of identical neural block techniques before compared with after operation have not documented clinically relevant differences in *post*operative analgesia or analgesic requirements. Several studies are available on *pre*operative neural block with local anaesthetics compared with no treatment and most studies have found a reduction in late postoperative pain, request for additional analgesics, or both, compared with no neural block [3, 20, 30, 32, 39]. However, these studies do not demonstrate that such effects result from optimal timing of analgesia or a reduction in central hyperexcitability by *pre*operative analgesic treatment. Other studies during greater surgical trauma (abdominal surgery) have not been able to show that intense *pre*operative extradural analgesia followed by 1–4 days continuous extradural treatment with combinations of local anaesthetics and opioids has any long-lasting effect on *post*operative pain during rest or mobilization compared with no neural block [34, unpublished observations].

The difference between the effect of pre-emptive analgesia on postinjury nociceptive processing in experimental studies and pain in clinical studies may have several explanations. Although central sensitization may contribute to postoperative pain in humans, surgical trauma differs from the conditioning stimuli applied in most experimental studies. Contrary to a well-localized thermal or chemical injury, or brief C-afferent stimulation, the afferent input to the CNS during and after surgery is prolonged and extensive, with mixed cutaneous, muscular and visceral components. Central sensitization may be generated not only during surgery, but also in the postoperative period, because of persistent inflammation and hyperalgesia at the wound site. Thus intraoperative nociceptive block may not be adequate to reduce postoperative sensitization of central neurones. Recently, we have demonstrated more efficient reduction in secondary hyperalgesia to a burn injury in volunteers by a pre-burn block compared with an identical post-burn block, thus confirming experimental studies [unpublished observations]. However, this difference was significant only as long as the block was clinically effective [unpublished observations]. Furthermore, conventional analgesic methods (local anaesthetics or opioids) may not provide total C-afferent block during surgery. Thus the negative studies of pre- *vs* postoperative identical neural block [8, 12] or preoperative extradural block *vs* no block [34, unpublished observations] may be explained by insufficient afferent block. Thus several studies have documented that such blocks were ineffective in inhibiting potentials evoked by peripheral electrical stimulation [9, 28, 29] or the inflammatory response to surgery [34, 35]. Therefore, the optimal intensity, the duration and the timing of analgesia to prevent alterations in dorsal horn neurones after tissue injury of greater magnitude than that studied experimentally [4, 5, 10, 43, 44], need further investigation before clinical recommendations of pre-emptive analgesia can be established.

In conclusion, more, well designed clinical studies are needed to evaluate the clinical implications of the findings of central hyperexcitability and long-lasting analgesic effects of a pre-injury neural block in experimental studies. The exciting developments in our understanding of the biochemistry involved in the processing of nociceptive stimuli, based upon experimental studies, undoubtedly will have a major impact on the future treatment of acute pain. Prevention of the functional changes in the central nervous system by "pre-emptive analgesia" or other techniques, is a fascinating working hypothesis, but the definition of pre-emptive analgesia with regard to duration compared with the duration of the peripheral stimulus should be evaluated. Future, well designed clinical studies may clarify the relative importance of effective pre-emptive analgesia, compared with continuous analgesic treatment during the period when nociceptive impulses are generated from the wound, or if a combination of such efforts may provide improved pain relief without significant side effects. Finally, the effect of such regimens on the incidence of postsurgical chronic and neuropathic pain should be explored.

Note added in proof: In a recent study by Katz and colleagues, extradural fentanyl $4\ \mu g\ kg^{-1}$ was more effective when administered before compared with 15 min after surgical incision in patients undergoing thoracic surgery [45]. However, pain scores and postoperative morphine consumption were reduced only at one of five assessments (at 6 h and from 12 to 24 h after operation, respectively) during a 48-h study period. Furthermore, the pre-emptive study group was older and included more females than the control group, both of which factors may result in less pain and opioid consumption. Thus this study does not present evidence for a clinically significant effect of pre-emptive administration of opioids on postoperative pain.

REFERENCES

1. Bach S, Noreng MF, Tjellden NU. Phantom limb pain in amputees during the first 12 months following limb amputation, after preoperative lumbar epidural blockade. *Pain* 1988; **33**: 297–301.
2. Baumann TK, Simone DA, Shain CN, LaMotte RH. Neurogenic hyperalgesia: the search for the primary cutaneous afferent fibers that contribute to capsaicin-induced pain and hyperalgesia. *Journal of Neurophysiology* 1991; **66**: 212–227.
3. Bugedo GJ, Carcamo CR, Mertens RA, Dagnino JA, Munoz HR. Preoperative percutaneous ilioinguinal and iliohypogastric nerve block with 0.5% bupivacaine for post-herniorrhaphy pain management in adults. *Regional Anesthesia* 1990; **15**: 130–133.
4. Coderre TJ, Melzack R. Cutaneous hyperalgesia: contributions of the peripheral and central nervous systems to the increase in pain sensitivity after injury. *Brain Research* 1987; **404**: 95–106.
5. Coderre TJ, Vaccarino AL, Melzack R. Central nervous system plasticity in the tonic pain response to subcutaneous formalin injection. *Brain Research* 1990; **535**: 155–158.
6. Cousins MJ. Acute pain and the injury response: immediate and prolonged effects. *Regional Anesthesia* 1989; **14**: 162–179.
7. Dahl JB, Erichsen CJ, Fuglsang-Frederiksen A, Kehlet H. Pain sensation and nociceptive reflex excitability in volunteers and surgical patients. *British Journal of Anaesthesia* 1992; **69**: 117–121
8. Dahl JB, Hansen BL, Hjortsø N-C, Erichsen CJ, Møiniche S, Kehlet H. Influence of timing on the effect of continuous extradural analgesia with bupivacaine and morphine after major abdominal surgery. *British Journal of Anaesthesia* 1992; **69**: 4–8.
9. Dahl JB, Rosenberg J, Lund C, Kehlet H. Effect of thoracic epidural bupivacaine 0.75% on somatosensory evoked potentials after dermatomal stimulation. *Regional Anesthesia* 1990; **15**: 73–75.
10. Dickenson AH. A cure for wind up: NMDA receptor antagonists as potential analgesics. *Trends in Pharmacological Science* 1990; **11**: 307–309.
11. Dickenson AH, Sullivan AF. Subcutaneous formalin-induced activity of dorsal horn neurones in the rat: differential response to an intrathecal opiate administered pre or post formalin. *Pain* 1987; **30**: 349–360.
12. Dierking G, Dahl JB, Kanstrup J, Dahl A, Kehlet H. Effect of pre- *vs* postoperative inguinal field block on postoperative pain after herniorrhaphy. *British Journal of Anaesthesia* 1992; **68**: 344–348.
13. Dubner R. Neuronal plasticity and pain following peripheral

tissue inflammation or nerve injury. In: Bond MR, Charlton JE, Woolf CJ, eds. *Proceedings of the VIth World Congress on Pain*. Amsterdam: Elsevier, 1991; 263–276.

14. Dubner R, Ruda MA. Activity-dependent neuronal plasticity following tissue injury and inflammation. *Trends in Neuroscience* 1992; **15**: 96–103.
15. Dupuis R, Lemay H, Bushnelle MC, Duncan GH. Preoperative flurbiprofen in oral surgery: A method of choice in controlling postoperative pain. *Pharmacotherapy* 1988; **8**: 193–200.
16. Ejlersen E, Andersen HB, Eliasen K, Mogensen T. A comparison between pre- and postincisional lidocaine infiltration on postoperative pain. *Anesthesia and Analgesia* 1992; **74**: 495–498.
17. Ekblom A, Hansson P. Thermal sensitivity is not changed by acute pain or afferent stimulation. *Journal of Neurology, Neurosurgery and Psychiatry* 1987; **50**: 1216–1220.
18. Hansson P, Ekblom A, Lindblom U, Marchettini P. Does acute intraoral pain alter cutaneous sensibility? *Journal of Neurology, Neurosurgery and Psychiatry* 1988; **51**: 1032–1036.
19. Hardy JD, Wolff HG, Goodell H. Experimental evidence on the nature of cutaneous hyperalgesia. *Journal of Clinical Investigation* 1950; **29**: 115–140.
20. Jebeles JA, Reilly JS, Gutierrez JF, Bradley EL, Kissin I. The effect of pre-incisional infiltration of tonsils with bupivacaine on the pain following tonsillectomy under general anesthesia. *Pain* 1991; **47**: 305–308.
21. Kirsch JR, Diringer MN, Borel CO, Hanley DF, Merritt WT, Bulkley GB. Preoperative lumbar epidural morphine improves postoperative analgesia and ventilatory function after transsternal thymectomy in patients with myasthenia gravis. *Critical Care Medicine* 1991; **19**: 1474–1479.
22. Kiss IE, Kilian M. Does opiate premedication influence postoperative analgesia? A prospective study. *Pain* 1992; **48**: 157–158.
23. Koskinen R, Tigerstedt I, Tammisto T. The effect of peroperative alfentanil on the need for immediate postoperative pain relief. *Acta Anaesthesiologica Scandinavica* 1991; **35** (Suppl. 96): O21.
24. LaMotte RH, Lundberg LER, Torebjörk HE. Pain, hyperalgesia and activity in nociceptive C units in humans after intradermal injection of capsaicin. *Journal of Physiology (London)* 1992; **448**: 749–764.
25. LaMotte RH, Shain CN, Simone DA, Tsai EFP. Neurogenic hyperalgesia: psychophysical studies of underlying mechanisms. *Journal of Neurophysiology* 1991; **66**: 190–211.
26. Lewis T. *Pain*. New York: Macmillan, 1942.
27. Lund C, Hansen OB, Kehlet H. Effect of surgery on sensory threshold and somatosensory evoked potentials after skin stimulation. *British Journal of Anaesthesia* 1990; **65**: 173–176.
28. Lund C, Selmar P, Hansen OB, Hjortsø NC, Kehlet H. Effect of epidural bupivacaine on somatosensory evoked potentials after dermatomal stimulation. *Anesthesia and Analgesia* 1987; **66**: 34–38.
29. Lund C, Selmar P, Hansen OB, Kehlet H. Effect of intrathecal bupivacaine on somatosensory evoked potentials following dermatomal stimulation. *Anesthesia and Analgesia* 1987; **66**: 809–813.
30. McQuay HJ, Carroll D, Moore RA. Postoperative orthopaedic pain—the effect of opiate premedication and local anaesthetic blocks. *Pain* 1988; **33**: 291–295.
31. Mendell LM. Physiological properties of unmyelinated fiber projection to the spinal cord. *Experimental Neurology* 1966; **16**: 316–322.
32. Narchi P, Benhamou D, Fernandez H. Intraperitoneal local anaesthetics for shoulder pain after day-case laparoscopy. *Lancet* 1991; **338**: 1569–1570.
33. Raja SN, Campbell JN, Meyer RA. Evidence for different mechanisms of primary and secondary hyperalgesia following heat injury to the glabrous skin. *Brain* 1984; **107**: 1179–1188.
34. Schulze S, Roikjaer O, Hasselstrøm L, Jensen NH, Kehlet H. Epidural bupivacaine and morphine plus systemic indomethacin eliminates pain but not systemic response and convalescence after cholecystectomy. *Surgery* 1988; **103**: 321–327.
35. Schulze S, Rye B, Møller IW, Kehlet H. Influence of local anesthesia and local hypothermia on leucocyte, temperature and transferrin response to surgery. *Danish Medical Bulletin* 1992; **39**: 86–89.
36. Simone DA, Sorkin LS, Oh O, Chung JM, Owens C, LaMotte RH, Willis WD. Neurogenic hyperalgesia: central neural correlates in responses of spinothalamic tract neurons. *Journal of Neurophysiology* 1991; **66**: 228–246.
37. Smith CM, Guralnick MS, Gelfand MM, Jeans ME. The effect of transcutaneous electrical nerve stimulation on post-Cesarean pain. *Pain* 1986; **27**: 181–193.
38. Torebjörk E, Lundberg L, LaMotte R. Central changes in processing of mechanoreceptive input in capsaicin-induced secondary hyperalgesia in humans. *Journal of Physiology (London)* 1992; **448**: 765–780.
39. Tverskoy M, Cozacov C, Ayache M, Bradley EL, Kissin I. Postoperative pain after inguinal herniorraphy with different types of anesthesia. *Anesthesia and Analgesia* 1990; **70**: 29–35.
40. Wall PD. The prevention of postoperative pain. *Pain* 1988; **33**: 289–290.
41. Woolf CJ. Recent advances in the pathophysiology of acute pain. *British Journal of Anaesthesia* 1989; **63**: 139–146.
42. Woolf CJ. Central mechanisms of acute pain. In: Bond MR, Charlton JE, Woolf CJ, eds. *Proceedings of the VIth World Congress on Pain*. Amsterdam: Elsevier, 1991; 25–34.
43. Woolf CJ, Wall PD. Morphine-sensitive and morphine-insensitive actions of C-fibre input on the rat spinal cord. *Neuroscience Letters* 1986; **64**: 221–225.
44. Woolf CJ, Wall PD. Relative effectiveness of C primary afferent fibers of different origins in evoking a prolonged facilitation of the flexor reflex in the rat. *Journal of Neuroscience* 1986; **6**: 1433–1442.
45. Katz J, Kavanagh BP, Sandler AN, Nierenberg H, Boylan JF, Friedlander M, Shaw BF. Pre-emptive analgesia. Clinical evidence of neuroplasticity contributing to postoperative pain. *Anesthesiology* 1992; **77**: 439–446.

British Journal of Anaesthesia 1993; 70: 440–442

SHORT COMMUNICATIONS

COMPARISON OF NASAL CANNULAE WITH FACE MASK FOR OXYGEN ADMINISTRATION TO POSTOPERATIVE PATIENTS

K. M. NOLAN, J. A. WINYARD AND D. R. GOLDHILL

SUMMARY

Thirty postoperative patients were allocated randomly to receive oxygen by Hudson face mask at 4 litre min^{-1} (group I) or 2 litre min^{-1} (group II) via nasal cannulae. From 22:00 on the first night after operation, the position of the nasal cannula or face mask was observed for 8 h using video and oxyhaemoglobin saturation (Sp_{O_2}) recorded simultaneously. In group I the mask remained on and positioned correctly in five patients. In the 10 other patients it was removed a total of 28 times, 17 for nursing tasks, for a median time of 2 min 39 s (range 30 s to 7 h 40 min 40 s). In group II the nasal cannula was removed once in one patient for 16 min 38 s and eight times in another for a total of 1 h 18 min 7 s. Average Sp_{O_2} with mask on was 98% (range 96.1–99.9%), with mask off 95% (range 89.8–98.8%) and with cannula 97% (range 90.8–99.3%). We conclude that nasal cannulae are more likely to remain in position than face masks and maintain an adequate saturation in most patients. (Br. J. Anaesth. 1993; **70**: 440–442)

KEY WORDS

Equipment: face mask, nasal cannulae. Oxygen: postoperative administration.

Some patients experience episodes of hypoxaemia after abdominal surgery [1, 2] and supplementary oxygen by face mask may prevent these episodes [3]. However, in a previous study [4] we showed that a face mask is often removed for routine nursing tasks, and patients are frequently hypoxaemic during these periods of mask removal. When nasal cannulae are used, many nursing tasks, such as mouth care and temperature measurement, do not interfere with the delivery of oxygen. We therefore determined if nasal cannulae are more likely than face masks to remain positioned correctly and ascertained the effect of mask or cannula position on oxyhaemoglobin saturation (Sp_{O_2}).

METHODS AND RESULTS

After Ethics Committee approval and patient consent to video observation and pulse oximetry, 30 ASA I–III patients (six men) undergoing elective abdominal surgery were allocated randomly to two equal groups. Group I received oxygen by Hudson face mask at 4 litre min^{-1} and group II received oxygen 2 litre min^{-1} by nasal cannulae. In group I, mean age was 67 yr (range 47–82 yr) and mean weight 66 kg (range 49–102 kg). In group II, mean age was 50 yr (range 26–75 yr) and mean weight 72 kg (range 48–105 kg). Anaesthetic technique and postoperative analgesia were not standardized, but the majority of patients in each group (60–80%) received i.m. opioids. Correct placement of the mask or cannula was confirmed at the start of the 8-h period from 22:00 on the first night after operation and neither the patient nor the ward staff was aware of the purpose of the study. The technique used was identical to that of the previous study [4]. A video camera operating in ambient light was used to record the patient's face, the position of the mask or cannula and the time as indicated by a clock within the field of view. Sp_{O_2} was recorded with an Ohmeda 3700e pulse oximeter. The oximeter reading was sampled approximately every 15 s and the digital value placed into a computer spreadsheet. Patients were asked also if they found the mask or cannula comfortable, uncomfortable or a nuisance. The following were determined from review of the video recordings:

(1) The number of times that the nasal cannula or mask was removed or replaced and the associated events.

(2) The duration of time for which the cannula or mask was on or off.

(3) Changes in Sp_{O_2} with alterations in cannula or mask position.

In group I, the mask remained on continuously and positioned correctly in five patients. In the 10 other patients it was removed a total of 28 times (range 1–6 times per patient) and remained off for median time of 2 min 39 s (range 30 s to 7 h 40 min 40 s). In five patients on eight occasions, the mask was off for more than 10 min (median 54 min 47 s; range 13 min 26 s to 7 h 40 min 40 s). In group II, the nasal cannulae remained positioned correctly in 13 patients and were removed once in one patient for 16 min 38 s and eight times in the other for a total of 1 h 18 min 7 s (median 3 min 32 s; range 1 min 0 s to 50 min 8 s). One patient in group I had a lesser average Sp_{O_2} (85%) with the mask on than with it off

---

KATHLEEN M. NOLAN, M.B., B.CH., B.A.O., F.F.A.R.C.S.I.; JAMES A. WINYARD; DAVID R. GOLDHILL, M.A., M.B., B.S., F.R.C.ANAES.; The Anaesthetics Unit, The London Hospital Medical College, Whitechapel, London E1 1BB. Accepted for Publication: October 9, 1992.

TABLE I. *Events associated with oxygen mask removal*

Event	Total times mask removed (No.)	Average (range) time mask off for this event (h:min:s)	Time mask off for this event (% of total)
Mouth care	13	0:01:49 (0:00:30–0:04:48)	2
Removed by patient	9	01:00:00 (0:01:46–07:40:40)	46
Temperature observation	4	02:17:24 (0:01:15–06:18:48)	46
Vomiting/retching	2	0:35:16 (0:02:01–01:08:31)	6

(91 %). This patient's Sp_{O_2} was satisfactory at the start of the study period when the mask was on. After the patient was turned, Sp_{O_2} decreased and remained less than 90 % for approximately 4 h, despite the mask being positioned correctly. The patient slept for part of this time and was examined also by a doctor who auscultated the chest. When the mask was removed, Sp_{O_2} increased and remained between 90 % and 95 % when the mask was again replaced. One possible explanation is that the mask may have become disconnected from the oxygen source when the patient was turned initially. The oxygen outlet was, unfortunately, not within the view of the video. This patient has been excluded from analysis of Sp_{O_2} values. In the other patients, mask removal resulted in a median decrease in Sp_{O_2} of 2 % (range 0–8 %). In the two patients in whom the nasal cannula became displaced, Sp_{O_2} decreased by 1.3 % in the patient with a single removal and by a median of 2.3 % (range 0–5.5 %) in the other patient. Average Sp_{O_2} with the mask on was 98 % (range 96.1–99.9 %) and with the mask off 95 % (range 89.8–98.8 %). Average Sp_{O_2} with the cannula on was 97 % (range 90.8–99.3 %). In the two patients in whom the cannulae were removed, average Sp_{O_2} were 92 % and 99 % with the cannulae on and 91 % and 95 % with the cannulae off. In group I, Sp_{O_2} was $\leqslant$ 89 % for 2.4 % of the study period and the mask was off for 99.5 % of this time. In group II, Sp_{O_2} was $\leqslant$ 89 % for 2 % of the study and the nasal cannulae were off for 0.7 % of this time. In group I, Sp_{O_2} was $\geqslant$ 95 % for 87 % of the study time and the mask was on for 97.9 % of this time. In group II, Sp_{O_2} was $\geqslant$ 95 % for 82.6 % of the study time and cannulae were on for 100 % of this time. The events associated with mask removal are shown in table I.

The mask was removed for mouth care and temperature measurement on 17 occasions and accounted for approximately 50 % of the total time that the mask was off. The nasal cannulae were removed once for mouth care, seven times by the patient and once for the patient to get out of bed.

COMMENT

Hypoxaemia is a frequent occurrence in the 24 h after abdominal surgery [1, 2]. Supplementary oxygen by face mask can prevent these episodes of hypoxaemia [3]. However, in a previous study we observed that patients do not always receive the oxygen prescribed because the mask is often removed for routine nursing tasks such as mouth care and temperature measurement [4]. In this study, we have shown that nasal cannulae are more likely to remain in position than face masks. They do not have to be removed for mouth care and oral temperature measurement and can remain *in situ* during retching and vomiting. The duration of time that the mask remained off for nursing care was variable, ranging from 30 s to 6 h 18 min 48 s and accounted for approximately 50 % of the total time that the mask was off. Patient removal accounted for most of the remaining time that the mask was off. This was not reflected in the patients' assessment of mask comfort, as no patient found the mask uncomfortable, although 13 % of patients thought it a nuisance.

This study was carried out on the same wards as our earlier work [4] in which the mask remained on continuously and positioned correctly in only one of 20 patients. The nursing staff were unaware of the purpose of the studies and the improvement seen in mask placement in the present study may reflect a growing awareness of the importance of administering oxygen after operation. Specific instructions on the importance of mask placement may further improve mask positioning and this is now being investigated.

The average Sp_{O_2} with the cannulae on was 97 % and the average Sp_{O_2} for each patient was always greater than 90 % (range 90.8–99.3 %), so we can conclude that oxygen administered via nasal cannulae maintained an adequate Sp_{O_2} in the majority of patients. Previous work has shown that face masks, nasal catheters and nasal cannulae prevent postoperative hypoxaemia with equal success and that there is no significant difference between nasal cannula and mask [5]. The percentage of oxygen delivered to our two groups was not identical, but probably reflected clinical practice. An oxygen flow of 2 litre min^{-1} via mask or nasal catheter delivers a mean oropharyngeal oxygen concentration of 28 % and at 4 litre min^{-1} a mean concentration of 38 % [6]. Sixty percent of patients found the nasal cannula comfortable and 87 % of patients said the mask was comfortable. The cannulae used were simple plastic nasal prongs and the addition of a foam collar at the anterior nares, as described in a previous study [6], may increase patient acceptability. This study confirms that administering oxygen by face mask is unreliable. Nasal oxygen is of no benefit in patients with obstructed nasal passages. We did not attempt to assess nasal patency in our patients and nasal cannulae proved to be an effective way to deliver oxygen. They are cheaper than most masks and are acceptable to the majority of patients.

REFERENCES

1. Catley DM, Thornton C, Jordan C, Lehane JR, Royston D, Jones JG. Pronounced episodic oxygen desaturation in the postoperative period: Its association with ventilatory pattern and analgesic regime. *Anesthesiology* 1985; **63**: 20–28.
2. Rosenberg J, Dirkes WE, Kehlet H. Episodic arterial oxygen desaturation and heart rate variations following major abdominal surgery. *British Journal of Anaesthesia* 1989; **63**: 651–654.
3. Jones JG, Jordan C, Scudder C, Rocke DA, Barrowcliffe M. Episodic postoperative oxygen desaturation: the value of added oxygen. *Journal of the Royal Society of Medicine* 1985; **78**: 1019–1022.
4. Nolan KM, Baxter MK, Winyard JA, Roulson CJ, Goldhill DR. Video surveillance of oxygen administration by mask in postoperative patients. *British Journal of Anaesthesia* 1992; **69**: 194–196.
5. Sellers WFS, Higgs CMB. Comparison of tracheal oxygen concentrations using Hudson mask, nasal cannula and nasal catheter. *Anesthesia and Analgesia* 1987; **66**: S153.
6. Fairfield JE, Goroszeniuk T, Tully AM, Adams AP. Oxygen delivery systems—a comparison of two devices. *Anaesthesia* 1991; **46**: 135–138.

British Journal of Anaesthesia 1993; 70: 443–445

RELATIONSHIP BETWEEN VOLUME OF DISTRIBUTION OF ATRACURIUM AND BODY WEIGHT

C. J. R. PARKER AND J. M. HUNTER

SUMMARY

We have determined the central and steady state volumes of distribution of atracurium 0.25 mg kg^{-1} in 41 healthy adult patients. Volume of distribution, corrected for body weight (ml kg^{-1}), correlated negatively with body weight ($r = -0.612$ for central volume of distribution; $r = -0.737$ for the steady state volume of distribution). When expressed as an absolute volume, neither central nor steady state volume of distribution correlated significantly with body weight ($r = 0.120$ and $r = 0.131$, respectively). These data cast doubt upon the necessity for the dose of atracurium to be related to body weight in the healthy adult population. (Br. J. Anaesth. 1993; **70**: 443–445)

KEY WORDS

Neuromuscular relaxants: atracurium. Pharmacokinetics: body weight.

It is usual to administer non-depolarizing neuromuscular blocking drugs in a dose related to body weight, and to express volume terms in a pharmacokinetic analysis as a ratio to body weight, for example in the units ml kg^{-1}. It has been shown, however, that for pancuronium the volume of distribution is not correlated closely with body weight [1]. Beemer, Bjorksten and Crankshaw [2] reported the volume of distribution of atracurium at steady state during an i.v. infusion given to a series of 20 patients, and noted that the variability within the population increased when the estimates were "corrected" for total body weight.

The question arises as to the nature of the relationship between volume terms in the description of atracurium pharmacokinetics, and body weight. The aim of the present study was to describe the relationship between volume of distribution of atracurium and body weight in healthy adults, who were studied as part of a project to determine the relationship between the pharmacokinetics and pharmacodynamics of atracurium.

METHODS AND RESULTS

Patients and anaesthesia

We studied 41 healthy patients undergoing minor surgery requiring the use of neuromuscular blocking drugs. The study was approved by the Ethics Committee of the Royal Liverpool Hospital and informed consent was obtained from all patients, who were studied in three groups, which differed only in the technique used to maintain anaesthesia.

The physical characteristics of the patients are summarized in table I. Other results from 38 of these patients have been reported previously [3]; the present series included three others in addition, in whom electromyographic recordings were technically unsatisfactory.

Premedication consisted of either promethazine 50 mg or diazepam 10 mg, orally on the night before surgery, or cyclizine 37.5–50 mg with morphine 7.5–10 mg i.m. 1 h before surgery. Premedication was omitted in those patients admitted to hospital on the day of surgery.

Anaesthesia was induced with fentanyl 25–200 µg and thiopentone 250–500 mg, and maintained with 66% nitrous oxide in oxygen. In group one this was supplemented with 0.9% isoflurane end-tidal; in group two supplementation was with 0.5% halothane end-tidal; in a third group no volatile anaesthetic agent was used, but midazolam 3–10 mg i.v. was given. End-tidal concentrations of volatile anaesthetic agents were monitored using an infra-red analyser (Datex Normac).

After induction of anaesthesia, electromyographic monitoring of the adductor pollicis of one hand was undertaken with a Medelec MS6. Two i.v. cannulae were sited: one for withdrawal of blood samples, the other for administration of atracurium.

After a period of 20 min during which the end-tidal concentration of volatile anaesthetic agent (if used) was stabilized, atracurium 0.25 mg kg^{-1} was given by constant rate infusion over a period of 10 min. Ventilation was controlled and the trachea intubated when appropriate; end-tidal carbon dioxide partial pressure was maintained in the range 4.0–5.3 kPa (Datex Capnomac). Pharmacological antagonism of neuromuscular block was not used.

Measurement of plasma concentrations of atracurium

Heparinized blood samples (2.5 ml) were taken before and at 1, 2, 4, 6, 8 and 10 min after the start of the infusion, and at 1, 2, 4, 6, 8, 10, 15, 20, 25, 30,

---

C. J. R. PARKER, M.A., M.D., F.R.C.ANAES.; J. M. HUNTER, M.B., CH.B., F.R.C.ANAES.; University Department of Anaesthesia, 4th Floor, Royal Liverpool Hospital, Prescot Street, P.O. Box 147, Liverpool L69 3BX. Accepted for Publication: October 16, 1992.

TABLE I. *Physical characteristics and pharmacokinetic results of the patients in each of the three groups (mean (range or* SD)). *No statistically significant difference in pharmacokinetic variables between the groups* ($P > 0.05$)

	Isoflurane ($n = 15$)	Halothane ($n = 16$)	Midazolam ($n = 10$)
Age (yr)	37.0 (19.7–65.1)	37.8 (21.6–54.7)	37.3 (15.3–57.2)
Weight (kg)	63.7 (11.2)	68.2 (7.6)	66.8 (14.2)
Sex (M:F)	8:7	8:8	4:6
Compartmental analysis			
V_1 (litre)	4.48 (0.65)	4.00 (0.76)	3.94 (0.69)
β (min^{-1})	0.038 (0.006)	0.035 (0.005)	0.036 (0.005)
α (min^{-1})	0.26 (0.12)	0.23 (0.05)	0.24 (0.06)
$k_{21}+k_{20}$ (min^{-1})	0.10 (0.04)	0.09 (0.02)	0.09 (0.02)
Non-compartmental analysis			
Vd^{ss} (litre)	8.71 (0.70)	8.00 (1.02)	7.97 (1.26)

40, 50, 60, 75 and 90 min after the end of the infusion. The plasma was frozen rapidly and stored at −20 °C until subsequent analysis by HPLC, using the method described in detail previously [3]. Plasma concentrations were measured in duplicate, with a coefficient of variation typically less than 6 % (range 1.6–11.1 %).

Data analysis

In order to obtain an estimate of the central volume of distribution, equations arising from a two-compartment pharmacokinetic model with elimination from both compartments were fitted to the plasma concentration profile using non-linear, least squares regression. The Gauss–Newton algorithm was used to define the least squares solution, with each datum point weighted as its inverse. The fit was implemented by a program written by the authors in Microsoft "Quickbasic" v4.0, and run on an 8086-based IBM-compatible personal computer. A two-compartment model was preferred to a simpler one-compartment model in all cases using the F test of residual variance (values of F ranged from 19.1 (2, 37 d.f.) to 1193 (2, 38 d.f.)). The individual rate constants of a two-compartment model with elimination from both compartments are not identifiable; the following combination of parameters was identified:

V_1 = central volume of distribution
α = hybrid distribution rate constant
β = hybrid elimination rate constant
$k_{21}+k_{20}$ = sum of exit rate constants from the peripheral compartment.

In order to obtain a measure of total volume of distribution, the steady state volume of distribution (Vd^{ss}) was estimated using the standard non-compartmental formula [4]:

$$Vd^{ss} = \left[\frac{\text{infused dose}}{\text{AUC}}\right] \cdot \left[\frac{\text{AUMC}}{\text{AUC}} - \frac{T}{2}\right]$$

where AUC = area under the curve; AUMC = area under the first moment curve.

Linear correlations were evaluated with Pearson's product–moment correlation coefficient.

The profile of mean plasma concentration for 38 of the 41 patients has been illustrated previously [3].

The mean central and steady state volumes of distribution, for each group are shown in table I, as absolute values. The central volume of distribution, expressed as an absolute volume (in litre) is plotted against body weight in figure 1. There was no significant correlation ($r = +0.120, n = 41, P > 0.1$).

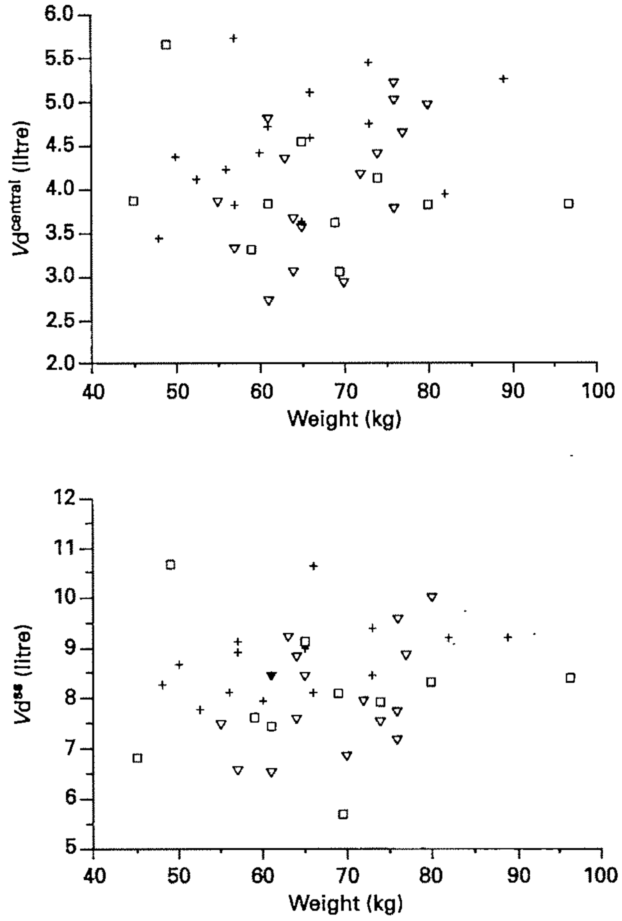


FIG. 1. Volume of distribution (in litre) plotted against body weight for isoflurane (+), halothane (▽) and midazolam (□). Upper panel: central volume of distribution; lower panel: steady state volume of distribution. No significant correlation is evident between each measure of volume of distribution and body weight ($r = +0.120$ for central volume of distribution; $r = +0.131$ for steady state volume of distribution).

Similarly, the steady state volume of distribution (expressed in litre) did not correlate significantly with body weight ($r = +0.131, n = 41, P > 0.1$) (fig. 1).

When the central and steady state volumes of distribution were normalized for body weight (units ml kg^{-1}) there was a highly significant negative correlation of both measures of volume of distribution with body weight: central volume of distribution $r = -0.612$, $P < 0.0001$; steady state volume of distribution $r = -0.737$, $P < 0.0001$.

COMMENT

Although the pharmacokinetics of atracurium have been studied extensively in the adult patient, the volume of distribution (the ratio of the amount of drug present to the plasma concentration) has generally been expressed in the units ml kg^{-1}. This practice can be justified only if the volume of distribution is proportional to body weight. It has been noted, within one population studied by Beemer, Bjorksten and Crankshaw [2], that the variance of the estimated steady state volume of distribution is increased on division of the absolute volume by body weight.

The present results are similar to those obtained for pancuronium by McLeod, Hull and Watson [1], who showed that volume of distribution, estimated by either V^{β} or V^{ss}, did not correlate significantly with body weight. The negative correlations between volume of distribution in ml kg^{-1} and weight presently reported simply represent the negative correlation of weight with its inverse. Their strength does, however, emphasize that the use of an inappropriate correction for body weight complicates rather than simplifies the comparison of results from subjects of differing weights. It is possible that this may have reduced the power of previous studies in which the volumes of distribution of groups of subjects were compared on an ml kg^{-1} basis.

Clearly, the present results apply only within the adult range in which they were obtained. Some relationship between body size and volume of distribution presumably exists in children but, although Brandom and colleagues were careful to consider an appropriate correction for body size in this group [5], it is not clear that this should be body weight. Indeed, volume terms were more nearly comparable between infants and children when comparison was based on body surface area.

One corollary of the present finding is that, if atracurium is administered in a dose related to body weight (that is, a fixed mg kg^{-1} dose), a relatively greater plasma concentration may be produced in heavier than in lighter adults; presumably, the drug may therefore achieve a greater effect. In a retrospective study in which the dose requirement for tubocurarine was judged on clinical grounds [6], Dundee showed that the dose administered during the first 2 h of anaesthesia was not related closely to body weight. Furthermore, division of the dose given by body weight did not diminish significantly the interindividual variability in the dose given.

The finding that the volume of distribution is independent of body weight is consistent with the water solubility of the drug and the fact that at least some of the variation in body weight between healthy adults is a result of variation in adiposity. The result cannot be extrapolated to more lipophilic drugs.

In retrospect, it would have been desirable to have assessed the physique of the present series of patients more thoroughly, for example with the use of skinfold thickness, to ascertain if it is possible to derive an index of body size which is related closely to the volume of distribution of atracurium. It does, however, remain clear that body weight is an unsuitable measure.

REFERENCES

1. McLeod K, Hull CJ, Watson MJ. Effects of ageing on the pharmacokinetics of pancuronium. *British Journal of Anaesthesia* 1979; **51**: 435–438.
2. Beemer GH, Bjorksten AR, Crankshaw DP. Pharmacokinetics of atracurium during continuous infusion. *British Journal of Anaesthesia* 1990; **65**: 668–674.
3. Parker CJR, Hunter JM. Dependence of the neuromuscular blocking effect of atracurium upon its disposition. *British Journal of Anaesthesia* 1992; **68**: 555–561.
4. Gibaldi M, Perrier D. *Pharmacokinetics*, 2nd Edn. New York: Marcel Dekker, 1982.
5. Brandom BW, Stiller RL, Cook DR, Woelfel SK, Chakravorti S, Lai A. Pharmacokinetics of atracurium in anaesthetized infants and children. *British Journal of Anaesthesia* 1986; **58**: 1210–1213.
6. Dundee JW. The relationship of the dosage of d-tubocurarine chloride and laudolissin to body weight, sex and age. *British Journal of Anaesthesia* 1954; **26**: 174–181.

British Journal of Anaesthesia 1993; 70: 446–448

PIPECURONIUM-INDUCED PROLONGATION OF VECURONIUM NEUROMUSCULAR BLOCK

I. SMITH AND P. F. WHITE

SUMMARY

*We have examined the prolongation of a maintenance dose of vecuronium after an intubating dose of pipecuronium in 45 patients who received either pipecuronium 70 µg kg^{-1} or vecuronium 200 µg kg^{-1} i.v. for tracheal intubation, followed by either pipecuronium 10 µg kg^{-1} or vecuronium 15 µg kg^{-1} for maintenance of neuromuscular block. The duration of the vecuronium maintenance dose was greater after pipecuronium (40 (*SD *12) min) than after vecuronium (29 (9) min) (*P = 0.02*). The duration of pipecuronium after pipecuronium (49 (15) min) was similar to that of vecuronium after pipecuronium. We conclude that the duration of action of vecuronium is prolonged by prior administration of pipecuronium.* (Br. J. Anaesth. 1993; **70**: 446–448)

KEY WORDS

Neuromuscular relaxants: pipecuronium, vecuronium. Neuromuscular transmission: prolongation.

Pipecuronium bromide (Arduan) is a new non-depolarizing neuromuscular blocking drug, structurally similar to both vecuronium and pancuronium. Pipecuronium is comparable in duration of action to pancuronium, but is devoid of vagolytic actions [1]. Because of this long duration, anaesthetists might consider changing to a shorter acting neuromuscular blocker for subsequent maintenance doses—possibly vecuronium because it has cardiovascular properties similar to those of pipecuronium [1]. As the action of vecuronium is prolonged significantly after pancuronium [2, 3], we have examined the interaction between pipecuronium and vecuronium during balanced anaesthesia.

METHODS AND RESULTS

After approval by the Washington University School of Medicine Human Studies Committee, we studied 50 patients who gave informed consent. Healthy, ASA I or II patients, aged 18–65 yr were allocated to one of three groups according to a computer-generated random number sequence. Group 1 received pipecuronium for intubation and maintenance of neuromuscular block, group 2 received pipecuronium and then vecuronium, and group 3 received vecuronium throughout. Exclusion criteria included a body weight 30% greater than ideal values, chronic antibiotic therapy, neuromuscular disorders and abnormal reactions to myoneural blocking drugs.

All patients received midazolam 1–5 mg i.v. (for sedation and anxiolysis) before operation. Anaesthesia was induced with sufentanil 0.5–1.0 µg kg^{-1} and thiopentone 2–4 mg kg^{-1} i.v. Neuromuscular activity was monitored by electromyography (EMG) (NMT monitor 221, Datex medical instrumentation, Tewksbury, Massachusetts). Silver–silver chloride adhesive gel electrodes (AMI 1750, Medtronic, Andover Medical, Haverhill, Massachusetts) were applied as described previously [4], with the recording electrode over the body of the first dorsal interosseous muscle and the reference electrode over its insertion. Baseline measurements were obtained after loss of consciousness. The distal ulnar nerve was stimulated with a supramaximal (70-mA) square wave of 100 µs duration at 2 Hz, every 20 s. Groups 1 and 2 received pipecuronium 70 µg kg^{-1} i.v., and group 3 received vecuronium 200 µg kg^{-1} i.v.

Anaesthesia was maintained with a variable rate infusion of sufentanil 0.2–0.5 µg kg^{-1} h^{-1} and 60–70% nitrous oxide in oxygen. Isoflurane 0.2–0.5% (end-expired) was added to maintain haemodynamic stability (mean arterial pressure within 20% of pre-incisional value). Additional neuromuscular blocker was administered when the first twitch (T1) of the train-of-four returned to 25% of baseline: group 1 received pipecuronium 10 µg kg^{-1}, and groups 2 and 3 received vecuronium 15 µg kg^{-1}. Additional maintenance doses were administered when T1 again returned to 25% of baseline. Heart rate, non-invasive arterial pressure, end-tidal carbon dioxide partial pressure and volatile agent concentration, and oesophageal and peripheral temperatures were monitored continuously.

After discontinuation of sufentanil and isoflurane, residual neuromuscular block was antagonized with edrophonium 1 mg kg^{-1} and atropine 7–10 µg kg^{-1} i.v. Baseline drift was defined as failure of T1 to return to $\geqslant 80\%$ of the value before block, after adequate antagonism of the neuromuscular block (T4/T1 > 70%).

IAN SMITH, B.SC., M.B., B.S., F.R.C.ANAES.; PAUL F. WHITE*, PH.D., M.D., F.F.A.R.A.C.S., Department of Anesthesiology, Washington University School of Medicine, St Louis, MO 63110, U.S.A.

Accepted for Publication: November 6, 1992.

*Present address, for correspondence: Department of Anesthesiology and Pain Management, University of Texas Southwestern Medical Center, 5323 Harry Hines Boulevard, Dallas, Texas 75235-9068, U.S.A.

TABLE I. *Patient characteristics and perioperative factors which could influence the duration of neuromuscular block in the three treatment groups (number, mean (range or* SD*) or median (range))*

	Pipecuronium–pipecuronium ($n = 17$)	Pipecuronium–vecuronium ($n = 15$)	Vecuronium–vecuronium ($n = 13$)
Age (yr)	44 (19–59)	53 (35–63)	52 (33–60)
Weight (kg)	75 (11)	77 (12)	72 (9)
Height (m)	1.74 (0.06)	1.75 (0.11)	1.71 (0.06)
ASA physical status (I/II)	6/11	4/11	7/6
Sex (M/F)	11/6	11/4	8/5
Serum creatinine concn (mg dl^{-1})	1.0 (0.2)	0.9 (0.2)	1.0 (0.2)
Preoperative midazolam (mg)	2.4 (1.1)	1.9 (0.6)	2.6 (1.1)
Total sufentanil (μg)	149 (54)	171 (77)	139 (81)
Mean end-tidal isoflurane (%)	0.31 (0.14)	0.39 (0.11)	0.35 (0.13)
Mean end-tidal CO_2 (kPa)	6.0 (0.5)	5.9 (0.4)	5.7 (0.4)
Central temperature (°C)	36.2 (0.5)	35.9 (0.6)	35.8 (0.5)
Peripheral temperature (°C)	35.4 (1.0)	35.6 (0.6)	35.0 (1.4)
Median duration of procedure (min)	247 (105–518)	213 (175–499)	196 (113–373)
Median blood loss (ml)	750 (50–3000)	1025 (200–3000)	1000 (150–1400)
Median fluid replacement (ml)	4000 (1800–7900)	4100 (2450–7200)	4000 (1800–5200)

Data were analysed with the Stata statistical program, using analysis of variance for comparisons of continuous variables and chi-square test for discrete variables. Changes in continuous variables with time were analysed using paired t tests. Bonferroni's correction was applied to multiple comparisons. Data are expressed as mean (SD) (SE in graphs) unless stated otherwise. $P < 0.05$ was considered statistically significant.

Five patients were excluded from data analysis because of baseline drift. There were no significant differences in patient variables between the three groups (table I). Similarly, there were no differences in anaesthetic requirements or physiological factors likely to influence the duration of neuromuscular block (table I). Heart rate and arterial pressure did not differ between the groups at any time. Complete neuromuscular block was achieved after the intubating dose in all patients. The clinical duration (time for T1 to return to 25% of baseline) of the intubating dose of pipecuronium was 112 (36) min and 120 (33) min for groups 1 and 2, respectively, but only 89 (19) min for vecuronium ($P = 0.01$).

After pipecuronium (group 1), the duration of the first maintenance dose of pipecuronium was 49 (15) min. This was significantly greater than the duration of the first maintenance dose of vecuronium after vecuronium in group 3 (29 (9) min) ($P = 0.0004$). The duration of the same maintenance dose of vecuronium after pipecuronium (group 2) was significantly greater (40 (12) min) ($P = 0.02$) than that of vecuronium after vecuronium (group 3), and not significantly different from that of pipecuronium in group 1 ($P = 0.09$).

A subset of 12 patients (four, five and three in groups 1, 2 and 3, respectively) received multiple maintenance doses of neuromuscular blocking drugs. The duration of action (fig. 1) remained constant in patients receiving the same blocking drug for intubation and maintenance (groups 1 and 3). In contrast, when vecuronium followed pipecuronium (group 2), there was a significant, progressive decline in duration with each of the first three maintenance doses ($P = 0.03$). However, even after four maintenance doses, the duration was still significantly prolonged compared with group 1 (fig. 1).

COMMENT

When vecuronium is used after previous administration of pipecuronium, its effect is prolonged significantly and its duration of action becomes similar to that of pipecuronium (when administered in the manufacturer's recommended maintenance doses). This is consistent with the previously reported interaction between vecuronium and pancuronium [2, 3]. When T1 returns to 25% of baseline, 70–80% of receptors are still occupied by neuromuscular blocker, and the maintenance dose need occupy only the vacant receptors to suppress T1. As the majority of receptors remain occupied by the drug administered initially, the clinical duration depends more on the kinetics of the first drug than on those of the maintenance (supplementary) drug. With subsequent doses, a progressively smaller proportion of the receptor sites are occupied by the original neuromuscular blocker and the degree of prolongation of action should decline with time. After pancuronium, the first two maintenance doses of vecuronium were reported to be prolonged; however, this was negligible by the third dose [3]. After pipecuronium, we detected clinically significant prolongation after four vecuronium doses, although the number of patients in this subset was small. The clinical implication is that, when pipecuronium has been administered, there is no obvious benefit (in terms of shorter duration) in using vecuronium for maintenance of neuromuscular block.

We used the EMG in this study because of its simplicity, reliability and lack of susceptibility to patient position and mechanical factors. Evoked EMG correlates well with the results of force transduction in the assessment of neuromuscular

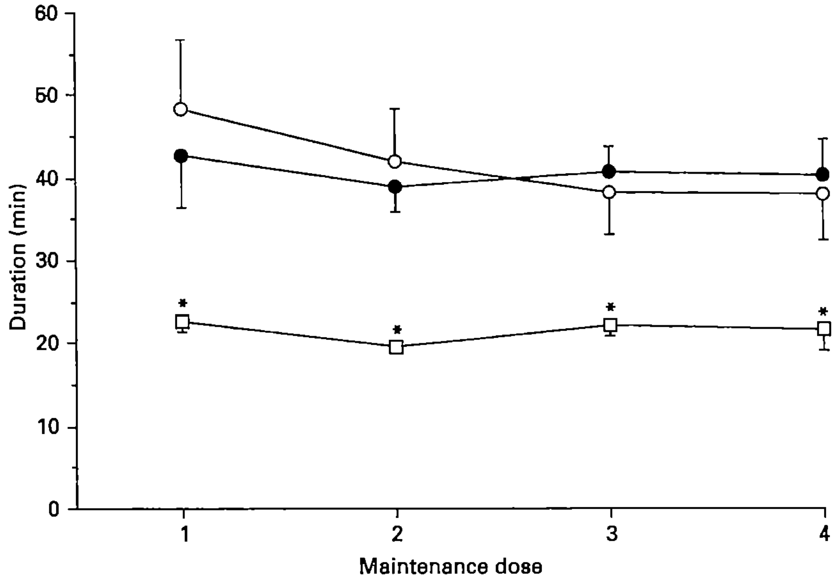


FIG. 1. Changes in the duration of action of maintenance doses of pipecuronium 10 μg kg^{-1} (group 1: ●, $n = 4$) or vecuronium 15 μg kg^{-1} (group 2: ○, $n = 5$; group 3: □, $n = 3$) over time (mean, SE). * $P < 0.05$ compared with groups 1 and 2.

block [4]. The major problem with the EMG is occasional failure of T1 to recover to baseline values (baseline drift), the mechanism of which is unknown [5]. We therefore excluded any patient in whom T1 did not return to within 20 % of baseline after antagonism of block with an anticholinesterase. Perioperative factors known to affect the duration of neuromuscular block or the accuracy of its measurement (e.g. carbon dioxide concentration and temperature) were similar in all three groups.

This study attempted to reflect the clinical conditions under which neuromuscular blocking drugs are frequently used. Doses were based on the manufacturer's recommendations, with the exception of the intubating dose of vecuronium, which was chosen in an attempt to achieve a duration of action approximately similar to that of pipecuronium 70 μg kg^{-1}. Although volatile anaesthetics may potentiate neuromuscular blocking drugs (for example, 0.9 % isoflurane decreases pipecuronium ED_{95} by 30 % [6]), the relatively small end-tidal concentration used in our study (0.35 (0.13) %) should have had minimal effects. Indeed, we found no correlation between duration of block and isoflurane concentration within the range used in this study.

In summary, pipecuronium was found to prolong the effect of subsequent doses of vecuronium such that standard maintenance doses of vecuronium and pipecuronium had similar durations of action. Although this potentiation decreased over time, it persisted for at least four maintenance doses. Consequently, there appears to be no advantage in using vecuronium as a maintenance agent after initial administration of pipecuronium.

ACKNOWLEDGEMENTS

We thank Robert M. Niecestro, PH.D., for his advice on the use of pipecuronium, Renee Johnson C.R.N.A., for her advice on the use of the Datex Relaxograph monitor and our research nurse, Linda Kratz, B.A.

REFERENCES

1. Foldes FF, Nagashima H, Nguyen HD, Duncalf D, Goldiner PL. Neuromuscular and cardiovascular effects of pipecuronium. *Canadian Journal of Anaesthesia* 1990; 37: 549–555.
2. Rashkovsky OM, Agoston S, Ket JM. Interaction between pancuronium bromide and vecuronium bromide. *British Journal of Anaesthesia* 1985; 57: 1063–1066.
3. Kay B, Chestnut RJ, Sum Ping JST, Healy TEJ. Economy in the use of muscle relaxants. Vecuronium after pancuronium. *Anaesthesia* 1987; 42: 277–280.
4. Carter JA, Arnold R, Yate PM, Flynn PJ. Assessment of the Datex relaxograph during anaesthesia and atracurium-induced neuromuscular blockade. *British Journal of Anaesthesia* 1986; 58: 1447–1452.
5. Smith DC. Central enhancement of evoked electromyographic monitoring of neuromuscular function. *British Journal of Anaesthesia* 1991; 66: 562–565.
6. Pittet J, Tassonyi E, Morel DR, Gemperle G, Richter M, Rouge J. Pipecuronium-induced neuromuscular blockade during nitrous oxide–fentanyl, isoflurane, and halothane anesthesia in adults and children. *Anesthesiology* 1989; 71: 210–213.

British Journal of Anaesthesia 1993; 70: 449–450

EFFECT OF RADIANT HEAT ON THE METABOLIC COST OF POSTOPERATIVE SHIVERING

A. SHARKEY, R. H. GULDEN, J. M. LIPTON AND A. H. GIESECKE

SUMMARY

Hypothermia and postoperative shivering are uncomfortable and may be dangerous. This study demonstrates that postoperative shivering may be controlled quickly and effectively with radiant heat, thereby reducing oxygen consumption and increasing thermal comfort. (Br. J. Anaesth. 1993; **70**: 449–450)

KEY WORDS

Metabolism. Complications: shivering. Temperature.

Postoperative shivering occurs in a significant number of patients in modern recovery rooms and it may increase oxygen consumption by as much as 400% [1]. If the oxygen demand induced by postoperative shivering exceeds the ability of depressed respiratory and circulatory systems to deliver oxygen to tissues, a relative oxygen debt or "demand hypoxia" can result, placing poorly perfused tissues at risk of ischaemia.

When applied to the blush area (the face, neck and upper chest regions that have a high density of thermoreceptors and sensitivity to warmth) radiant heat was found to inhibit shivering in obstetric patients [2] and in healthy volunteers [3] without significant side effects. The present study was designed to determine the influence of such local application of radiant heat on the metabolic consequences of postoperative shivering.

METHODS AND RESULTS

After approval by the local institutional Review Board, we studied 19 visibly shivering patients who had undergone Caesarean section or tubal ligation (ASA I or II; ages 18–40 yr (mean 26.7 (SEM 1.4) yr); weight 55–96 kg (mean 73.9 (2.5) kg), body surface area 1.49–1.94 m^2 (mean 1.74 (0.3) m^2) after operation in the recovery room. Anaesthesia was performed under spinal block (seven radiant heat and three control patients), extradural block (one radiant heat, four control) or combined spinal–extradural block (three radiant heat, one control). All patients received Bicitra 15 ml orally 45 min before operation; and diazepam 10 mg orally was given to those patients undergoing tubal ligation. All nine Caesarean sections were performed under combined spinal–extradural or extradural anaesthesia using 0.75% hyperbaric bupivacaine 1.5–1.8 ml, followed by plain 0.5% bupivacaine 3 ml mixed with fentanyl 200 µg, injected into the extradural space via an indwelling catheter. All extradural catheters were removed after operation. Fentanyl 50–100 µg was administered i.v. after delivery to provide additional pain control. The remaining 10 patients underwent tubal ligation under spinal anaesthesia (5% lignocaine 70 mg in 7.5% glucose). All patients received fentanyl 50–100 µg i.v. during surgery.

By means of a table of random numbers, the shivering patients were allocated to receive either radiant heat or warmed blankets after operation. Each patient was covered with a canopy connected to a Deltatrac Metabolic Monitor (Sensormatic; Yorba Linda, CA) which continuously sampled expired gases and calculated oxygen consumption and carbon dioxide production. Arterial pressure, Sp_{O_2}, and ECG (lead II) were monitored continuously.

After 10 min of baseline observation, patients received either radiant heat or warmed blankets. Six infra-red bulbs (750 W) arranged in two rows were suspended 45 cm above the sternum to illuminate the blush region, which was covered with one layer of lightweight cotton cloth. Skin temperature was monitored constantly via dual thermistors applied to the chest, providing autofeedback regulation of power to the lamps; the temperature was maintained at 41 ± 0.1 °C to prevent thermal injury. After a 10-min warming period, the heat lamps were switched off and recordings were continued for an additional 10 min.

All data were subjected to statistical analysis using repeated-measure ANOVA and Tukey's protected t test (two-tail), with $P < 0.05$ considered significant. The two groups were not statistically different in weight, height, body surface area, age, anaesthetic or temperature on arrival in the recovery room. The absolute $\dot{V}o_2$ is shown in figure 1.

Baseline (shivering) oxygen consumption in the radiant heat and warmed blankets groups was not statistically different ($P > 0.05$). However, with the application of radiant heat, $\dot{V}o_2$ significantly de-

---

AIDAN SHARKEY, M.B., B.CH., B.A.O., F.F.A.R.C.S.I.; RICHARD HEATH GULDEN, M.D.; JAMES M. LIPTON, PH.D.; ADOLPH H. GIESECKE, M.D.; Department of Anesthesiology, The University of Texas Southwestern Medical School, 5323 Harry Hines Blvd, Dallas, Texas 75235-9068, U.S.A. Accepted for Publication: November 2, 1992.

Correspondence to A.H.G.

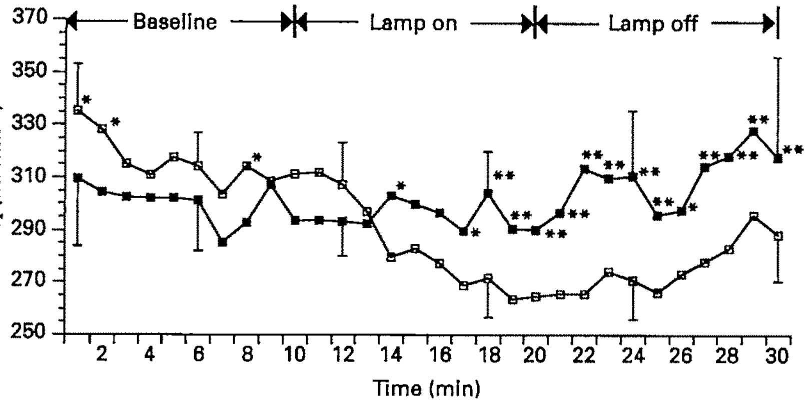


FIG. 1. Effect of radiant heat on postoperative oxygen consumption ($\dot{V}o_2$) in shivering patients. □ = Radiant heat group; ■ = control group. *$P < 0.05$; **$P < 0.01$ between groups.

creased ($P < 0.01$), whereas it remained increased in the warmed blankets group.

All radiant heat patients ceased visible shivering within 5 min of application of the heat and stated that they felt more comfortable. When the lamp was turned off, six of the eight patients resumed shivering and requested that the lamp be turned on again. Oxygen consumption increased in radiant heat patients, but did not return to baseline. All patients warmed with blankets complained of cold.

COMMENT

Intraoperative hypothermia was documented as a clinical entity more than 100 years ago [4]. Since then, many measures have been recommended to prevent heat loss during surgery and anaesthesia [5] but, despite this, the cold patient is still an "accepted concomitant" of postoperative recovery [6]. Such hypothermia is a primary factor in postoperative shivering.

Postoperative shivering may occur when the CNS temperature control systems emerge from anaesthesia and react to "cold" signals from thermoreceptors, which then initiate shivering, a thermogenic response.

Marked increases in oxygen consumption can occur in postoperative shivering, with an accompanying increase in postoperative morbidity and mortality. Our study demonstrates that postoperative shivering can be quickly and effectively controlled by warming the "blush" region and radiant heat. This treatment decreases oxygen consumption and, thus, reduces the immediate risks to cardiovascular and respiratory systems.

REFERENCES

1. Horvath SM, Spurr GB, Hutt BK, Hamilton LH. The metabolic cost of shivering. *Journal of Applied Physiology* 1956; 8: 595–602.
2. Sharkey A, Lipton JM, Murphy MT, Giesecke AH. Inhibition of post-anesthetic shivering with radiant heat. *Anesthesiology* 1987; 66: 249–252.
3. Mekjavik IB, Eiken O. Inhibition of shivering in man by thermal stimulation of the facial area. *Acta Physiologica Scandinavica* 1985; 125: 633–637.
4. Dastre A. *Les Anesthétiques: Physiologie et Applications Chirurgicales*. Paris: Masson, 1890; 317.
5. Flacke J, Flacke W. Inadvertent hypothermia: Frequent, insidious, and often serious. *Seminars in Anesthesia* 1983; 11: 183–196.
6. Ryan JF. Altered temperature regulation section two: Unintentional hypothermia. In: Cooperman LH, ed. *Complications in Anesthesiology*. Philadelphia: J. B. Lippincott, 1982; 284–313.

British Journal of Anaesthesia 1993; 70: 451–453

METABOLIC EFFECTS OF PROPOFOL AND FLUNITRAZEPAM GIVEN FOR SEDATION AFTER AORTIC SURGERY

F. MORITZ, J. PETIT, N. KAEFFER, G. OKSENHENDLER, H. PAPION, B. HECKETSWEILER, N. MOORE AND C. WINCKLER

SUMMARY

Sixteen patients who had undergone abdominal aortic surgery were allocated randomly to receive either propofol (total dose 3.2 (SEM 0.3) mg kg^{-1} h^{-1}) or flunitrazepam (total dose 15 (2) µg kg^{-1} h^{-1}) for 16 h after operation. Metabolic effects of sedation were assessed using a Deltatrac metabolic monitor. Initiation of sedation induced a 25% decrease in $\dot{V}O_2$ in both groups. The decrease was about 40% at 16 h. $\dot{V}O_2$ increased within 30 min after discontinuation of propofol and stabilized at values considerably less than the immediate postoperative value. A similar but slower increase was noted with flunitrazepam. While the propofol loading dose reduced the Buffington index and should therefore be avoided, no cardiovascular side effects were noted with the maintenance infusion. Weaning from ventilatory support was achieved within 15 (2) min and 264 (108) min after discontinuation of propofol and flunitrazepam, respectively. (Br. J. Anaesth. 1993; **70**: 451–453)

KEY WORDS

Anaesthetics, intravenous: propofol. Hypnotics, benzodiazepines: flunitrazepam. Metabolism: oxygen consumption. Recovery: postoperative sedation.

Oxygen consumption ($\dot{V}O_2$) increases after major surgical procedures in the early period of recovery from general anaesthesia [1, 2]. Short term sedation has been proposed to prevent the complications caused by this increase in $\dot{V}O_2$. Propofol can be used easily and safely in the ICU [2, 3]. However, it is not known if discontinuation of propofol, with subsequent brisk recovery, also induces a brisk increase in $\dot{V}O_2$.

This study was designed to compare metabolic and haemodynamic state during and after discontinuation of a 16-h postoperative sedation with either propofol or flunitrazepam.

METHODS AND RESULTS

After approval from the Institutional Ethics Committee and informed consent, we studied 16 ASA II–III stable patients who had undergone surgical treatment of infrarenal aortic aneurysm. Patients were allocated randomly to receive either propofol (group P) or flunitrazepam (group F) for 16 h, as soon as they responded to commands.

Anaesthesia had been induced with flunitrazepam 20 µg kg^{-1}, fentanyl 5 µg kg^{-1} and vecuronium 100 µg kg^{-1}, and maintained with intermittent administration of these agents combined with nitrous oxide and isoflurane.

Group P patients received an i.v. loading dose of propofol 2 mg kg^{-1} over 5 min followed by a continuous i.v. infusion of 3 mg kg^{-1} h^{-1}. In group F, the loading dose was flunitrazepam 0.02 mg kg^{-1} and the infusion 0.01 mg kg^{-1} h^{-1}. Boluses of drugs (propofol 1 mg kg^{-1} and flunitrazepam 0.015 mg kg^{-1}) were given to keep the patient at the required level of sedation (3–5 on Ramsay's scale). I.v. injections of morphine were allowed. Inotropic agents and vasodilators were given as required.

Ventilatory support was continued for the period of sedation, using a CPU 1 ventilator (Ohmeda Lab.). $\dot{V}O_2$, carbon dioxide production ($\dot{V}CO_2$) and respiratory quotient (RQ) were measured at the bedside using a Deltatrac metabolic monitor (Datex, Helsinki, Finland). After sedation was discontinued, the trachea was extubated if the following criteria had been met: total recovery, effective spontaneous breathing ($V_T > 10$ ml kg^{-1}, ventilatory frequency 10–25 b.p.m., $Pa_{O_2} \geq 10.7$ kPa and $Pa_{CO_2} \leq 6.7$ kPa), haemodynamic stability. Additional measurements were made using the canopy. Measurements were recorded immediately before sedation (T0), during sedation (at 30 min (T0.5) and 1 h (T1), 3 h (T3), 9 h (T9) and 12 h (T12)), immediately before discontinuation of sedation (T16 = TE) and for the following 2 h (TE+0.5, TE+1 and TE+2).

Measured $\dot{V}O_2$ was compared with the theoretical resting $\dot{V}O_2$ values, calculated using the Combes equations. Energy expenditure was calculated using the simplified Weir equation, and compared with the basal energy expenditure calculated using the Harris and Benedict equations. The rate–pressure product (RPP = HR × SAP; if greater than 12000, myo-

---

F. MORITZ, M.D.; J. PETIT, M.D.; N. KAEFFER, M.D.; G. OKSENHENDLER, M.D., PH.D.; H. PAPION, M.D.; C. WINCKLER, M.D.; Département d'Anesthésie–Réanimation Chirurgicale, Hôpital Charles Nicolle, 76031 Rouen-Cédex, France. B. HECKETSWEILER, PHARM.D., PH.D., Groupe de Biochimie et Physiopathologie Digestive et Nutritionnelle, Faculté de Médecine–Pharmacie de Rouen, avenue de l'Université, 76800 Saint Etienne du Rouvray, France. N. MOORE, M.D., PH.D., Laboratoire de Pharmacologie, Hôpital de Boisguillaume, 147, avenue du Maréchal Juin, 76230 Boisguillaume, France. Accepted for Publication: October 9, 1992.

Correspondence to J.P.

TABLE I. *Metabolic and haemodynamic criteria before and during the infusion and after discontinuation of propofol (P) or flunitrazepam (F) for postoperative sedation.* *P < 0.05 *within group compared with T0;* †P < 0.05 *within group compared with TE;* §P < 0.05, *between-group comparison of changes from TE*

	$\dot{V}O_2$ (ml min^{-1})		$\dot{V}CO_2$ (ml min^{-1})		Rate–pressure product		Buffington index	
Time	P	F	P	F	P	F	P	F
T0	355 (28)	383 (38)	265 (18)	270 (31)	14480 (1202)	12538 (1971)	1.46 (0.16)	1.47 (0.14)
T0.5	272 (29)*	284 (38)*	219 (20)*	224 (29)*	11722 (986)*	10932 (1574)	1.05 (0.12)*	1.28 (0.08)*
T1	243 (21)*	283 (38)*	197 (10)*	217 (30)*	10599 (657)*	11781 (1199)	1.24 (0.08)*	1.26 (0.07)*
T3	250 (16)*	278 (33)*	192 (11)*	198 (18)*	10712 (584)*	11575 (1177)	1.22 (0.08)*	1.33 (0.08)*
T6	241 (23)*	265 (25)*	193 (14)*	181 (12)*	11575 (696)*	12150 (1449)	1.20 (0.06)*	1.32 (0.09)*
T9	226 (15)*	261 (24)*	183 (11)*	182 (12)*	11594 (802)*	12212 (1224)	1.17 (0.07)*	1.25 (0.11)*
T12	221 (18)*	259 (25)*	183 (13)*	182 (13)*	11061 (815)*	11450 (966)	1.19 (0.07)*	1.24 (0.10)*
TE	214 (18)*	254 (24)*	168 (10)*	183 (17)*	11119 (770)*	11100 (916)	1.23 (0.05)*	1.27 (0.09)*
TE+0.5	252 (13)*†§	238 (21)*	197 (6)*†	187 (17)*	12100 (1240)*	11344 (807)	1.18 (0.06)*	1.26 (0.08)*
TE+1	255 (13)*†§	256 (22)*	204 (6)*† §	185 (14)*	12144 (814)* §	10970 (871)	1.17 (0.06)*	1.23 (0.10)*
TE+2	251 (16)*†	274 (33)*	206 (8)†	200 (25)*	12016 (795)*	11401 (902)	1.19 (0.08)*	1.23 (0.11)*

cardial ischaemic risk present) [4] and the Buffington index (BI = MAP/HR; if less than 1, risk present) [5] were calculated. Plasma concentrations of adrenaline and noradrenaline were assayed at TE and TE+2. Times from discontinuation of sedation to complete recovery and to tracheal extubation were noted.

Results (mean (SEM)) were compared using ANOVA, with $P < 0.05$ significant.

Groups were similar in age, weight, height, sex and temperature course of the patients, surgical procedure and total amounts of anaesthetic and postoperative drugs administered. Time between completion of surgery and initiation of sedation (2.27 (0.10) h in group P and 2.10 (0.15) h in group F), and T0 values of the studied variables were not statistically different.

Total doses were propofol 3.2 (0.3) mg kg^{-1} h^{-1} and flunitrazepam 15 (2) µg kg^{-1} h^{-1}. One patient (from group F) required one morphine injection (5 mg) at T1.

Metabolic and haemodynamic data are shown in table I. During sedation, $\dot{V}O_2$ changes were not statistically different in the two groups. The loading dose induced a 25% decrease in $\dot{V}O_2$. $\dot{V}O_2$ decreased further by 15% for the sedation period to reach its smallest value at TE. In group P, $\dot{V}O_2$ values were significantly greater at TE+0.5 than at TE and later remained unchanged. In group F, $\dot{V}O_2$ increased more slowly, with a significant difference only between TE+0.5 and TE+2. Measured $\dot{V}O_2$ values were 156%, 94% and 110% of theoretical resting $\dot{V}O_2$ values at T0, TE, and TE+2, respectively, in group P, and 168%, 111% and 120% in group F.

$\dot{V}CO_2$ did not differ between groups. The decrease in energy expenditure between T0 and TF amounted to 35%. Baseline energy expenditure was similar in the two groups (20.1 (0.9) kcal kg^{-1} day^{-1} in group P and 19.4 (1.3) kcal kg^{-1} day^{-1} in group F). Compared with baseline values, measured energy expenditure was 181 (14)% at T0, 110 (7%) at TE, 125 (7)% at TE+0.5 and 127 (7)% at TE+2 in group P. Corresponding values in group F (176 (11)%, 118 (6)%, 112 (6)% and 125 (8)%) were not significantly different.

All patients received 5% glucose which provided a 400–450 kcal day^{-1} energy supply; an additional 200–500 kcal were provided to group P patients, because of the propofol emulsion formulation. Compared with values at T0 (0.76 in group P; 0.73 in group F), RQ was significantly greater at T6 in group P (0.82) than in group F (0.70). Values later remained slightly but not significantly greater in group P (0.82–0.85) than in group F (0.70–0.79).

After the loading dose of propofol or flunitrazepam, heart rate did not change while systolic arterial pressure decreased significantly. During maintenance infusion, haemodynamics remained unchanged. Arterial pressures did not increase after sedation was discontinued. A significant decrease in RPP was noted in group P from T0.5 to TE+2. During sedation, RPP remained greater than 12000 in four group F and three group P patients. RPP did not change after discontinuation of sedation. Seven group P patients exhibited a decrease in BI after the loading dose, as a result of the decrease in mean arterial presure; the BI of two, close to 1 at T0, decreased transiently, to 0.64 and 0.43. In this group, BI later stabilized at greater than 1. In group F, BI also decreased, but remained in excess of 1.

Plasma concentrations of adrenaline at TE and TE+2 were within normal resting values (100 (50) pg ml^{-1}): 96.4 (56.4) pg ml^{-1} and 121.0 (59.9) pg ml^{-1} in group P, and 60.2 (17.5) pg ml^{-1} and 74.0 (20.8) pg ml^{-1} in group F. Plasma concentrations of noradrenaline showed a 2- or 3-fold increase from the normal range (400 (150) pg ml^{-1}): 1245.3 (453.1) pg ml^{-1} and 1273.0 (270.7) pg ml^{-1} in group P; 862.1 (129.6) pg ml^{-1} and 981.0 (184.0) pg ml^{-1} in group F at TE and TE+2, respectively. These values did not differ between the two groups.

Weaning after stopping sedation was achieved within 15 (2) min and 264 (108) min in groups P and F, respectively ($P < 0.001$). The time from discontinuation of sedation to tracheal extubation was dramatically shorter in group P (30 (3) min) than in group F (468 (153) min).

COMMENT

Because propofol has a rapid onset of action, rapid metabolism, and does not cumulate, continuous infusion has become popular for sedation of patients in the ICU [1–3]. The dose given in this study

(3.2 (0.3) mg kg^{-1} h^{-1}) was close to that used by Beller to maintain a value of 4 on Ramsay's scale in critically ill patients [3]. We compared propofol with flunitrazepam because flunitrazepam is the agent usually given in our ICU. Flunitrazepam has a rapid onset of action, but oversedation leading to delayed weaning from mechanical ventilation is a frequent side effect, as observed in our study.

Large plasma concentrations of noradrenaline were observed in both groups at the end of the period of sedation. Such increases are usual after major surgery as a part of the reaction to stress. As the stress response is not suppressed totally by opioids in usual clinical doses, it cannot be related to visceral pain only [6].

Indirect calorimetry provided immediate direct evidence of the metabolic benefits of sedation: both regimens decreased $\dot{V}O_2$ and energy expenditure by 25%: both variables were previously 1.6 to 1.7 times greater than predicted resting values. As hypnotics alter haemodynamic state, simultaneous measurement of oxygen delivery would have been necessary to assess any benefit of the decrease in $\dot{V}O_2$. At TE+1 and TE+2, $\dot{V}O_2$ remained close to T+0.5 values in the two groups. These results differ from those of Dumont and colleagues [1], who reported a brisk increase in $\dot{V}O_2$ to the postoperative presedation value soon after discontinuation of propofol. However, Dumont and colleagues' procedure was based on a shorter sedation time than ours and $\dot{V}O_2$ was measured over a 5-min period only, 5 min after the infusion was stopped.

RQ variations were not important. However, values in group P were transiently significantly greater, suggesting storage of fat from the propofol emulsion.

During postoperative sedation, infusion rates of hypnotic agents must be adjusted to avoid both oversedation and awakening. Our data suggest that bedside indirect calorimetry might be useful to decide when initiation of sedation is appropriate and to monitor it. Waiting for total recovery from general anaesthesia before initiating sedation allows full assessment of the patient, but it may be deleterious from a metabolic point of view and requires an initial loading dose, which may be risky in some patients.

ACKNOWLEDGEMENTS

The generous supply of the Deltratrac metabolic monitor by Datex Instr. is gratefully acknowledged. F.M. is a recipient of an ICI Award.

REFERENCES

1. Dumont JC, Guidon-Attalic, Viviand X, Akaga R, Churlaud C, François G. Effet de la sédation par propofol sur la consommation d'oxygène en période post-opératoire précoce. *Annales Françaises d'Anesthésie et de Réanimation* 1989; **8**: 10.
2. McMurray TJ, Collier PS, Carson IW, Lyons SM, Elliott P. Propofol sedation after open heart surgery. A clinical and pharmacokinetic study. *Anaesthesia* 1990; **45**: 322–326.
3. Beller JP, Pottecher T, Lugnier A, Mangin P, Otteni JC. Prolonged sedation with propofol in ICU patients: recovery and blood concentration changes during periodic interruptions in infusion. *British Journal of Anaesthesia* 1988; **61**: 583–588.
4. Cokkinos DV, Vorodis EM. Constancy of pressure–rate product in pacing-induced angina pectoris. *British Heart Journal* 1976; **38**: 39–42.
5. Buffington CW. Hemodynamic determinants of ischemic myocardial dysfunction in the presence of coronary stenosis in dogs. *Anesthesiology* 1985; **63**: 651–662.
6. Kehlet H. The stress response to anaesthesia and surgery: release mechanisms and modifying factors. *Clinical Anaesthesia* 1984; **2**: 315–339.

British Journal of Anaesthesia 1993; 70: 454–455

HEPATIC ELIMINATION OF DIAZEPAM: INTERACTIONS WITH ALBUMIN, DESFLURANE AND SEVOFLURANE

O. DALE, E. J. FRINK, L. THOMMESEN AND A. J. GANDOLFI

SUMMARY

We have studied the effect of sevoflurane and desflurane on the hepatic elimination of diazepam, by incubating slices of rat livers in a closed system. Protein free and protein containing (albumin 10 g litre^{-1}) buffers were used to examine the effect of the anaesthetics on enzyme activity and diazepam binding to albumin. Both anaesthetics (in concentrations of 0.5, 1.5 and 3.0 mmol litre^{-1}) reduced the elimination of diazepam slightly in the absence of albumin, while the presence of the protein increased elimination to a maximum of 30% at the greatest concentration of the anaesthetics. These data support previous observations that volatile anaesthetics may interact pharmacokinetically with both liver enzyme activity and drug binding to albumin. (Br. J. Anaesth. 1993; **70**: 454–455)

KEY WORDS

Anaesthetics, volatile: desflurane, isoflurane. Biotransformation: diazepam, enzyme activity. Interactions.

It has been reported previously that volatile anaesthetics and albumin may interact *in vitro* with the elimination of diazepam in rat liver by interference with both enzyme activity and drug–protein binding [1]. Apparently, enflurane increased the rate of diazepam elimination in the presence of albumin by displacing the drug, while the elimination rate was decreased slightly in the absence of the protein [1]. In contrast, isoflurane had no effect on these processes. Halothane caused the most marked reduction in diazepam elimination in the absence of albumin, probably as a result of inhibition of hepatic drug metabolizing enzymes.

In the present study, we have examined the effects of sevoflurane and desflurane on the elimination of diazepam with and without albumin in the rat liver slice model.

METHODS AND RESULTS

Sevoflurane and desflurane were obtained from the Maruishi Pharmaceutical Co. (Osaka, Japan) and Anaquest (Madison, WI, U.S.A.), respectively. Human serum albumin (Sigma A-1653) was purchased from Sigma Chemical Co (St Louis, MO, U.S.A.). Diazepam and prazepam were obtained from Roche-Norge A/S, Oslo, Norway.

The experimental and analytical procedures have been described elsewhere [1, 2]. Briefly, livers were excised from male Sprague–Dawley rats killed by decapitation. Slices were prepared according to standard procedures and mounted on the inner wall of a stainless steel mesh cylinder. This cylinder was incubated with the buffer under constant rotation at 37 °C for 2 h in screw-capped incubation vials. The

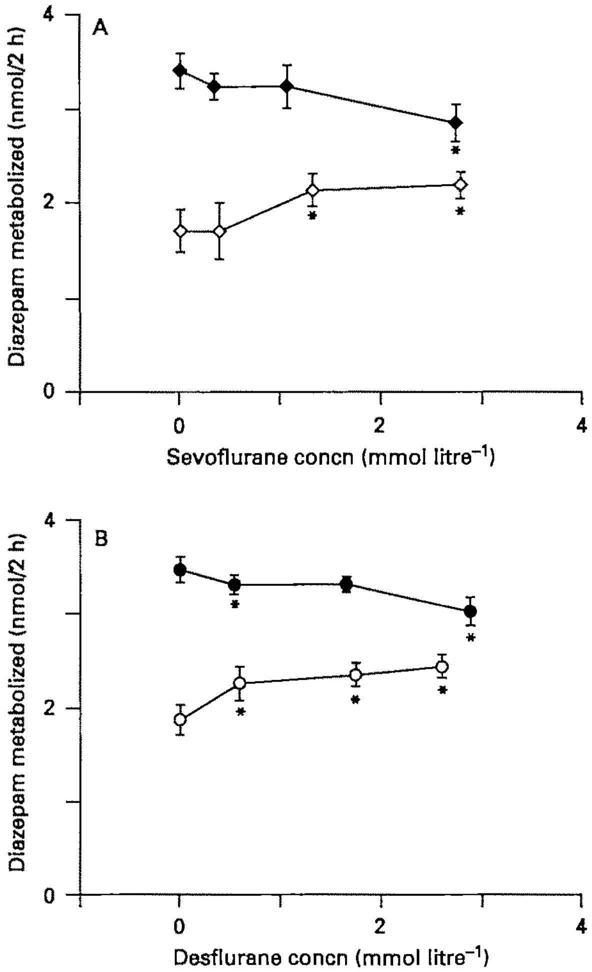


FIG. 1. Effect of sevoflurane (A) and desflurane (B) on the elimination of diazepam by rat liver slices at 37 °C for 2 h, with no albumin (filled symbols), or with albumin 10 g litre^{-1} (open symbols). Each point (mean, SD) represents 10 vials from five separate rat livers. *Statistically different from control ($P < 0.05$).

OLA DALE, M.D., PH.D.; LIV THOMMESEN, B.SC.; University of Trondheim, Department of Pharmacology and Toxicology, University Clinic, 7005 Trondheim, Norway. EDWARD J. FRINK JR., M.D.; A. JAY GANDOLFI, PH.D.; University of Arizona, Department of Anesthesiology, Health Sciences Center, Tucson, AZ 85724, U.S.A. Accepted for Publication: October 9, 1992.

anaesthetics were injected through Teflon-coated screw-caps by microsyringes (Supelco Inc., Bellefonte, Pennsylvania, U.S.A.) to achieve approximate equimolar concentrations of 0.5, 1.5 and 3.0 mmol litre^{-1} in the buffer analysed as described by Ghantous and colleagues [3, 4]. Diazepam elimination was calculated from each vial by subtracting the final concentration from the initial (2.5 µmol litre^{-1}) concentration.

Results are presented as mean (SD). Groups were compared by ANOVA. $P < 0.05$ was considered significant (Fischer test) using StatView II (Abacus Inc, Berkeley, California).

In the absence of albumin, there was a small, but statistically significant concentration-dependent reduction (15 % at 3 mmol litre^{-1}) in hepatic elimination of diazepam with both anaesthetics (fig. 1).

The presence of albumin 10 mg ml^{-1} reduced hepatic elimination of diazepam by about 50 % compared with the controls. With the addition of sevoflurane, statistically significant increases in hepatic elimination of diazepam occurred with the larger concentrations (1.5 and 3 mmol litre^{-1}). Desflurane increased the elimination of diazepam at all concentrations. Both anaesthetics increased the elimination by almost 30 % with the greatest concentration.

COMMENT

We have found that both sevoflurane and desflurane reduced the hepatic elimination of diazepam in rat liver slices in the absence of albumin, probably caused by a slight inhibition of hepatic enzyme activity. The agents were far less potent than halothane in this respect, as they reduced the elimination of diazepam by 15 % in concentrations of approximately 3 mmol litre^{-1}; a similar reduction was produced by halothane 1 mmol litre^{-1} under the same experimental conditions [1].

As has been reported for enflurane [1], the most significant interaction observed was an increase in elimination of diazepam, in the presence of albumin, with both desflurane and sevoflurane. Hepatic uptake of diazepam is confined to the free fraction. The major binding protein of diazepam in serum is albumin. Its presence in the buffer therefore reduces hepatic uptake of diazepam and consequently also its elimination, as shown in this and previous studies [1, 5]. If an agent such as enflurane, capable of displacing diazepam from albumin [5] is added to the buffer, increased elimination of diazepam results [1]. It seems likely, therefore, that the increased elimination of diazepam caused by the agents in the presence of albumin, particularly by desflurane, may be explained by an anaesthetic-induced increased free fraction of diazepam. It is worth noting that the real increase in elimination caused by diazepam displacement is not merely 30 %, but approximately 45 %, because of the 15 % reduction in enzyme activity that occurred in the absence of albumin.

What is the clinical relevance of our findings? Clinical anaesthesia with sevoflurane results in serum concentrations of about 0.5–0.7 mmol litre^{-1} [6], which is close to the smallest concentrations used here. When desflurane is used for clinical anaesthesia, the blood concentrations are thought to be in the same range as those for sevoflurane [7]. It seems unlikely, therefore, on the basis of our data, that sevoflurane may undergo any clinically relevant pharmacokinetic interactions with diazepam, but this cannot be ruled out for desflurane.

REFERENCES

1. Dale O, Gandolfi AJ, Brendel K, Schuman S. Rat liver slices and diazepam metabolism: *In vitro* interactions with volatile anaesthetic drugs and albumin. *British Journal of Anaesthesia* 1988; **60**: 692–696.
2. Dale O, Holten T, Nørkov T. Rat liver slices: Metabolic changes during short-term incubation in glucose-free buffer. *Pharmacology and Toxicology* 1990; **67**: 89–90.
3. Ghantous HN, Fernando J, Gandolfi AJ, Brendel K. Minimal biotransformation and toxicity of desflurane in guinea pig liver slices. *Anesthesia and Analgesia* 1991; **72**: 796–800.
4. Ghantous HN, Fernando J, Gandolfi AJ, Brendel K. Sevoflurane is biotransformed by guinea pig liver slices but causes minimal cytotoxicity. *Anesthesia and Analgesia* 1992; **75**: 436–440.
5. Dale O, Nilsen OG. Displacement of some basic drugs from human serum proteins by enflurane, halothane and their major metabolites. An *in vitro* study. *British Journal of Anaesthesia* 1984; **56**: 557–561.
6. Frink EJ, Malan TP, Atlas M, Domingues LM, DiNardo JA, Brown BR jr. Clinical comparison of sevoflurane and isoflurane in healthy subjects. *Anesthesia and Analgesia* 1992; **74**: 241–245.
7. Boban M, Stowe DF, Buljubasic N, Kampine JP, Bosnjak ZJ. Direct comparative effects of isoflurane and desflurane in isolated guinea pig hearts. *Anesthesiology* 1992; **76**: 775–780.

British Journal of Anaesthesia 1993; 70: 456–458

ANAESTHETIC PROPERTIES OF DIMETHYLTHIOUREA†

D. D. KOBLIN, M. J. LASTER AND J. LIU

SUMMARY

We have examined dimethylthiourea, a potent scavenger of free radicals, for its anaesthetic properties in mice and rats. In mice, dimethylthiourea abolished the righting reflex at intraperitoneal doses greater than 1.5 mg g^{-1} bodyweight; in rats, it decreased the MAC value for isoflurane in a dose-dependent fashion. Dimethylthiourea 0.5 g kg^{-1} decreased isoflurane MAC by 23%; at a dose of 2.0–4.0 g kg^{-1}, it abolished the response to tail clamp. Doses of 4.0 g kg^{-1} were lethal in the presence of isoflurane. A serum concentration of dimethylthiourea approximately 1 mg ml^{-1} produced a 50% reduction in isoflurane MAC. These anaesthetic properties of dimethylthiourea may influence experimental studies that examine the biochemical and physiological properties of this agent. (Br. J. Anaesth. 1993; **70**: 456–458)

KEY WORDS

Anaesthetics, volatile: isoflurane. Pharmacology: dimethylthiourea. Potency, anaesthetic: ED_{50}.

1,3-Dimethylthiourea [$CH_3NHCSNHCH_3$] is a scavenger of hydroxyl radicals [1]. Its administration to animals reduces the cellular injury associated with the production of hydroxyl radicals in several tissues. For example, dimethylthiourea prevents granulocyte-mediated oxidant lung injury [1], reduces brain oedema and infarct size after middle cerebral artery occlusion [2], decreases hyperoxia-induced injury [3] and reduces myocardial infarct size after occlusion of the left anterior descending coronary artery [4].

We have found in earlier studies that dimethylthiourea given to mice impeded inactivation of the enzyme methionine synthase by nitrous oxide [5]. These experiments also revealed that this scavenger had a sedative effect that increased with increasing dose. In the present study, we have assessed the anaesthetic properties of dimethylthiourea, by measuring its ability to abolish the righting reflex in mice and to decrease the requirement for isoflurane in rats.

METHODS AND RESULTS

These investigations were approved by the Animal Studies Subcommittee at the Veterans Administration Medical Center. Adult male ICR mice (29–35 g) and adult male Sprague–Dawley rats (330–430 g) were studied.

Mice were given intraperitoneal (i.p.) injections of dimethylthiourea 1.25, 1.50, 1.75, and 2.0 mg/g body weight. The time between injection and loss of righting reflex was defined as the sleep onset time. Mice were considered to have lost their righting reflex if, when placed in a supine position, they did not completely right themselves three times within 60 s. The time between the loss and recovery of the righting reflex was defined as the sleep time. After awakening (recovery of righting reflex), mice were killed with 100% carbon dioxide and blood was removed from the inferior vena cava for analysis of dimethylthiourea. Values at each dose were derived from four to eight mice.

In order to assess the effect of dimethylthiourea on isoflurane MAC, rats were placed into individual Perspex cylinders, administered 2.5–3.0% atm isoflurane for 10 min, and removed transiently from the cylinders for i.p. injections of dimethylthiourea 0 (saline control), 0.5, 1.0, 2.0 or 4.0 g kg^{-1}. Six rats were examined for each dose. Each rat received the same volume of i.p. solution (2 ml/100 g body weight). Rats were returned to the cylinders, given approximately 1.6% isoflurane in oxygen for 1 h, and examined for purposeful movement in response to a tail clamp applied for 1 min. The first concentration of isoflurane tested prevented movement to the tail clamp stimulus in all rats. Isoflurane concentration was then decreased by approximately 20%, allowed to equilibrate for at least 15 min, and the tail clamp stimulus repeated. If movement occurred, the animal was killed with 100% carbon dioxide and blood was removed from the inferior vena cava for analysis of dimethylthiourea. If no movement occurred, the isoflurane concentration was again decreased and the rat was retested to the tail clamp stimulus after equilibration of isoflurane. MAC was calculated as the mean of the isoflurane concentrations that just permitted and prevented movement.

Observations were made by an individual who was blind to the dose of dimethylthiourea injected. Isoflurane was measured by infra-red analysis.

DONALD D. KOBLIN*, PH.D., M.D.; MICHAEL J. LASTER, D.V.M.; JIN LIU, M.D.; Departments of Anesthesia, Veterans Administration Medical Center, San Francisco, CA 94121, and University of California, San Francisco, CA 94143, U.S.A. Accepted for Publication: October 26, 1992.

*Address for correspondence: Anesthesiology Service (129), Veterans Administration Medical Center, 4150 Clement Street, San Francisco, CA 94121, U.S.A.

†A preliminary report of part of these results was published in *Anesthesiology* 1988; **69**: A616.

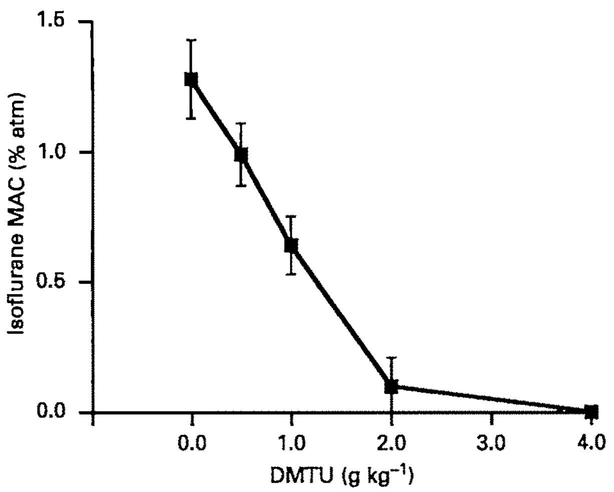


FIG. 1. Isoflurane MAC in rats given i.p. injections of dimethylthiourea (DMTU). Each point represents the results from six rats; error bars = SD. Four of six rats injected with DMTU 4.0 g kg^{-1} died during the course of the experiments.

Carbon dioxide concentrations were maintained less than 0.8% and rectal temperatures in the range 36.5–38.0 °C. Serum concentrations of dimethylthiourea were measured by gas chromatography [5]. All values are given as mean (SD).

At doses greater than 1.5 mg g^{-1}, dimethylthiourea consistently abolished the righting reflex in the mouse. Immediately after injection of dimethylthiourea, no sedative effect was noticeable. Mice remained spontaneously active and developed increasing degrees of ataxia about 10 min after injection (depending on the animal and the dose). Spontaneous activity decreased gradually with time until the animals eventually lost the ability to right themselves. No excitatory effects of dimethylthiourea could be detected. Increasing doses of the drug (1.5, 1.75 and 2.0 mg g^{-1}) were associated with shorter sleep onset times (87 (36.4) min, 36 (14.9) min and 31 (9.0) min), and sleep times increased (123 (88.5) min, 250 (57.4) min and > 600 min). Dimethylthiourea 1.25 mg g^{-1} did not consistently produce loss of righting reflex. In the two of eight animals that lost their righting reflex at this smallest dose, the sleep onset times exceeded 3 h. After dimethylthiourea 2.0 mg g^{-1}, unstimulated mice did not right themselves 10 h after the injection. Serum concentrations of dimethylthiourea at the time mice regained the righting reflex varied in the range 2.7–3.2 mg ml^{-1}.

Dimethylthiourea enhanced the potency of isoflurane in rats. Isoflurane MAC decreased from 1.28 (0.15) % in animals given i.p. injections of saline to 0.99 (0.12) % in rats injected with dimethylthiourea 0.5 g kg^{-1} ($P < 0.05$). Larger doses progressively decreased the requirement for isoflurane (fig. 1), with rats given 2 g kg^{-1} having an isoflurane requirement of 0.10 (0.11) %. Four of six rats given dimethylthiourea 4.0 g kg^{-1} died 1–3 h after starting isoflurane administration. The two other rats given the 4.0-g kg^{-1} dose did not respond positively to the tail clamp stimulus 20 min after the inspired isoflurane concentration was decreased to zero. The lower isoflurane MAC with increasing i.p. doses of dimethylthiourea corresponded to an increase in concentration of the scavenger in serum. After doses of dimethylthiourea 0.5, 1.0, 2.0, or 4.0 g kg^{-1}, its serum concentrations were 0.64 (0.15), 1.06 (0.15), 2.18 (0.18) and 3.96 (1.36) mg ml^{-1}, respectively.

COMMENT

Our results demonstrate that dimethylthiourea has anaesthetic properties. It consistently abolished the righting reflex in mice at doses greater than 1.5 mg g^{-1}—a reversible effect for a narrow range of doses. In the absence of inspired isoflurane (fig. 1), dimethylthiourea 4.0 g kg^{-1} also abolished the response to a tail clamp stimulus in rats. These anaesthetic doses of dimethylthiourea exceed the doses (typically 0.5 g kg^{-1}) used to ameliorate cellular injury [1–4]. However, the drug appeared to have a partial anaesthetic effect even at 0.5 g kg^{-1}, as this dose produced a 23% reduction in isoflurane MAC (fig. 1).

The anaesthetic properties of dimethylthiourea mimic those of a barbiturate. For example, as with dimethylthiourea, less thiopentone is needed to abolish the righting reflex than to prevent response to a stimulus to the tail. In common with dimethylthiourea, thiopentone reduces MAC for an inhaled agent in a dose-dependent fashion [6]. However, dimethylthiourea is approximately two orders of magnitude less potent than thiopentone as an anaesthetic. A 50% reduction in halothane MAC is produced at a thiopentone plasma concentration of 7.4 μg ml^{-1} [6], whereas a 50% reduction in isoflurane MAC was produced at a serum concentration of dimethylthiourea about 1 mg ml^{-1}. Thus, the anaesthetic properties of the latter (large doses and large serum concentrations required for anaesthesia; long sleep onset times after i.p. injection) are more similar to those of a barbiturate of low potency, such as barbitone, than to those of a barbiturate of high potency, such as thiopentone.

The finding that dimethylthiourea has anaesthetic properties has experimental implications. In studies that demonstrate a protective effect of dimethylthiourea (presumably related to scavenging of free radicals), appropriate controls need to be performed to show that the effect observed is a direct pharmacological action of the drug, rather than the effects of anaesthesia *per se* on the system.

ACKNOWLEDGEMENTS

Supported in part by NIA Grant P01 AG3104, a Merit Review Grant from the Veterans Administration, by a grant from the Academic Senate of the University of California at San Francisco, and by the UCSF Anesthesia Research Foundation. We thank Barbara W. Everman, M.S., for technical assistance.

REFERENCES

1. Fox RB. Prevention of granulocyte-mediated oxidant lung injury in rats by a hydroxyl radical scavenger, dimethylthiourea. *Journal of Laboratory Investigation* 1984; 74: 1456–1464.
2. Martz D, Beer M, Betz AL. Dimethylthiourea reduces ischemic brain edema without affecting cerebral blood flow. *Journal of Cerebral Blood Flow and Metabolism* 1990; 10: 352–357.

3. Beehler CJ, Simchuk ML, McCord JM, Repine JE. Effects of dimethylthiourea in hyperoxic injury. *Journal of Laboratory and Clinical Medicine* 1992; **119**: 508–513.
4. Carrea FP, Lesnefsky EJ, Repine JE, Shikes RH, Horwitz LD. Reduction of canine myocardial infarct size by a diffusible reactive oxygen metabolite scavenger. Efficacy of dimethylthiourea given at the onset of reperfusion. *Circulation Research* 1991; **68**: 1652–1659.
5. Koblin DD, Tomerson BW. Dimethylthiourea, a hydroxyl radical scavenger, impedes the inactivation of methionine synthase by nitrous oxide in mice. *British Journal of Anaesthesia* 1990; **64**: 214–223.
6. Stone DJ, Moscicki JC, DiFazio CA. Thiopental reduces halothane MAC in rats. *Anesthesia and Analgesia* 1992; **74**: 542–546.

British Journal of Anaesthesia 1993; 70: 459–461

CASE REPORTS

SPONTANEOUS EXCITATORY MOVEMENTS DURING RECOVERY FROM PROPOFOL ANAESTHESIA IN AN INFANT: EEG EVALUATION

A. BORGEAT, O. H. G. WILDER-SMITH, P. A. DESPLAND AND P. RAVUSSIN

SUMMARY

Spontaneous excitatory movements have been observed during recovery from propofol anaesthesia in children. Epilepsy has been postulated as a possible mechanism to explain these movements. We report the first case in which these spontaneous excitatory movements were studied using simultaneous multichannel EEG recordings. (Br. J. Anaesth. 1993; **70**: 459–461)

KEY WORDS

Anaesthetic techniques: intravenous. Anaesthetics intravenous: propofol. Complications: spontaneous excitatory movements.

Spontaneous excitatory movements have been observed during both induction and recovery from propofol anaesthesia [1–3]. Although there have been several case reports of "seizures" or opisthotonus during recovery from propofol anaesthesia [4–7] none of these has been evaluated by simultaneous EEG recordings.

An infant had exhibited spontaneous excitatory movements during recovery from previous propofol anaesthetics. In the course of a subsequent propofol anaesthetic, we were able to study these spontaneous excitatory movements using simultaneous multichannel EEG recordings.

CASE REPORT

The patient was a 6-week-old, otherwise healthy, 4-kg young girl. She was admitted for radiotherapy (35 courses of 3 min duration) of her congenital bilateral retinoblastoma. During the first two treatments, anaesthesia was performed with propofol. In the course of each recovery, spontaneous excitatory movements (graded stage 3 according to the previously described classification [3]) were observed, lasting 15–20 min until full awakening. The anaesthetic technique used was as follows: premedication with oral atropine 0.15 mg; local anaesthesia for venous cannulation (24-gauge) insertion using EMLA cream on the back of both hands. In the anaesthesia room, heart rate, arterial pressure and Sp_{O_2} were recorded. Anaesthesia was induced with a bolus of propofol 20 mg i.v. The lungs were ventilated manually with oxygen (FI_{O_2} 100 %). For the third course of radiotherapy, we decided to record the multichannel EEG during the phase of excitatory movements. After induction of anaesthesia (as described above) and completion of radiotherapy treatment, the child received a supplementary bolus of propofol 5 mg i.v. to facilitate placement of the EEG electrodes. Twelve intradermal needle electrodes were placed according to the 10–20 international system.

Electrode impedances were less than 6 kΩ. A CEM EEG recording machine (Vickers, U.K.) was used to record eight channels. The high frequency filter was set at 70 Hz; bipolar longitudinal montages were used. An ECG was recorded simultaneously on one channel.

Four minutes after the last bolus of propofol, the EEG recordings analysed by our specialist electroencephalographer, showed fast waves (10 Hz) with a mean voltage 50 µV coupled with theta waves (voltage 100–200 µV) (fig. 1). No spontaneous movements were noted. As the infant started to awake, excitatory movements involving the four limbs and the trunk appeared 7 min after the last dose of propofol. These movements were choreiform with extension, flexion and intermittent jerking of the limbs. They lasted up to 20 min until full awakening. The EEG recording during this period (7 min after last bolus of propofol) was characterized by blocking alpha-waves associated with symmetrical delta–theta waves (voltage 50–100 µV) (fig. 2). Spikes, spike-waves or other epileptogenic patterns were not observed. During the whole procedure, heart rate, arterial pressure and Sp_{O_2} (98–99 %) remained stable. The postoperative course was otherwise uneventful. The next day, an awake and asleep EEG were performed. These recordings were unremarkable. The same anaesthetic procedure coupled with an EEG recording was performed during the 23rd course of treatment. The results were similar to those reported above.

DISCUSSION

This is the first report of simultaneous continuous EEG recordings during spontaneous excitatory movements in an infant recovering from propofol anaesthesia. In this patient, the EEG recordings demonstrated deep anaesthesia with no signs of

---

A. BORGEAT, M.D.; O. H. G. WILDER-SMITH, M.D.; Department of Anaesthesiology, University Hospital of Geneva, 1211 Geneva 14, Switzerland. P. A. DESPLAND, M.D.; P. RAVUSSIN, M.D.; Department of Anaesthesiology, University Hospital of Lausanne, Switzerland. Accepted for Publication: October 9, 1992.

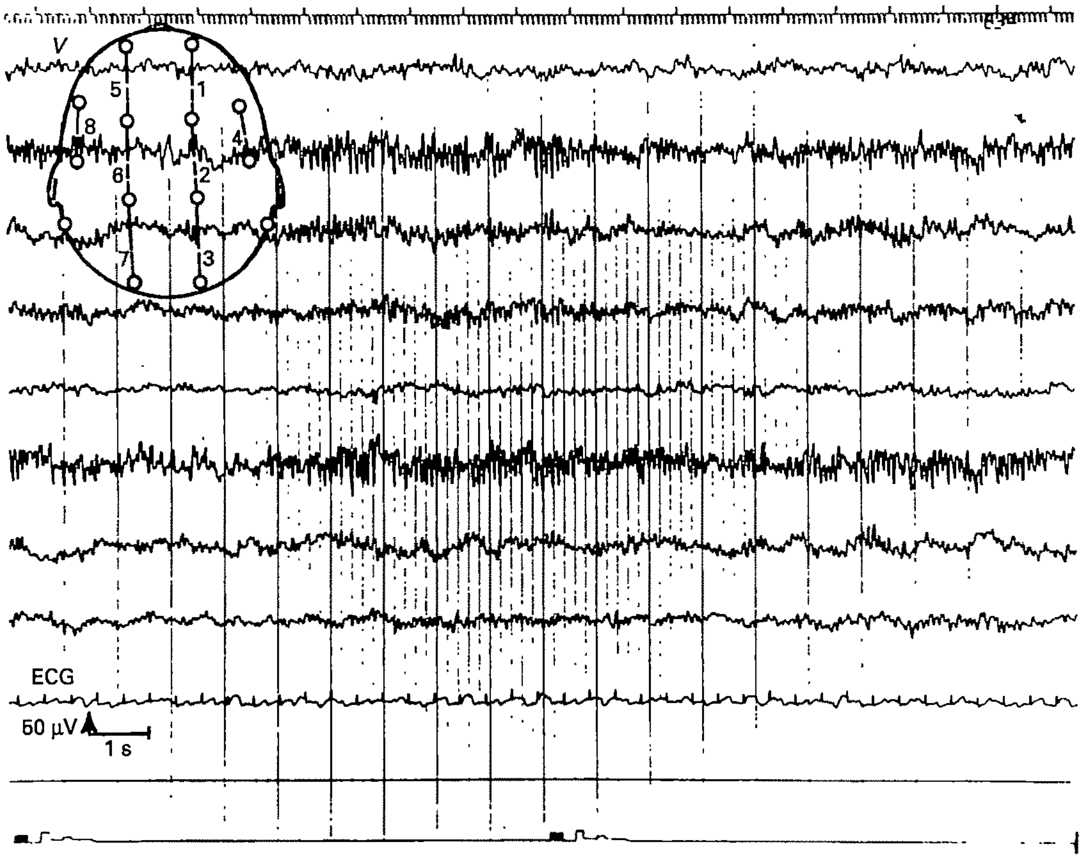


FIG. 1. EEG after induction demonstrating beta and theta activities: no spontaneous excitatory movements.

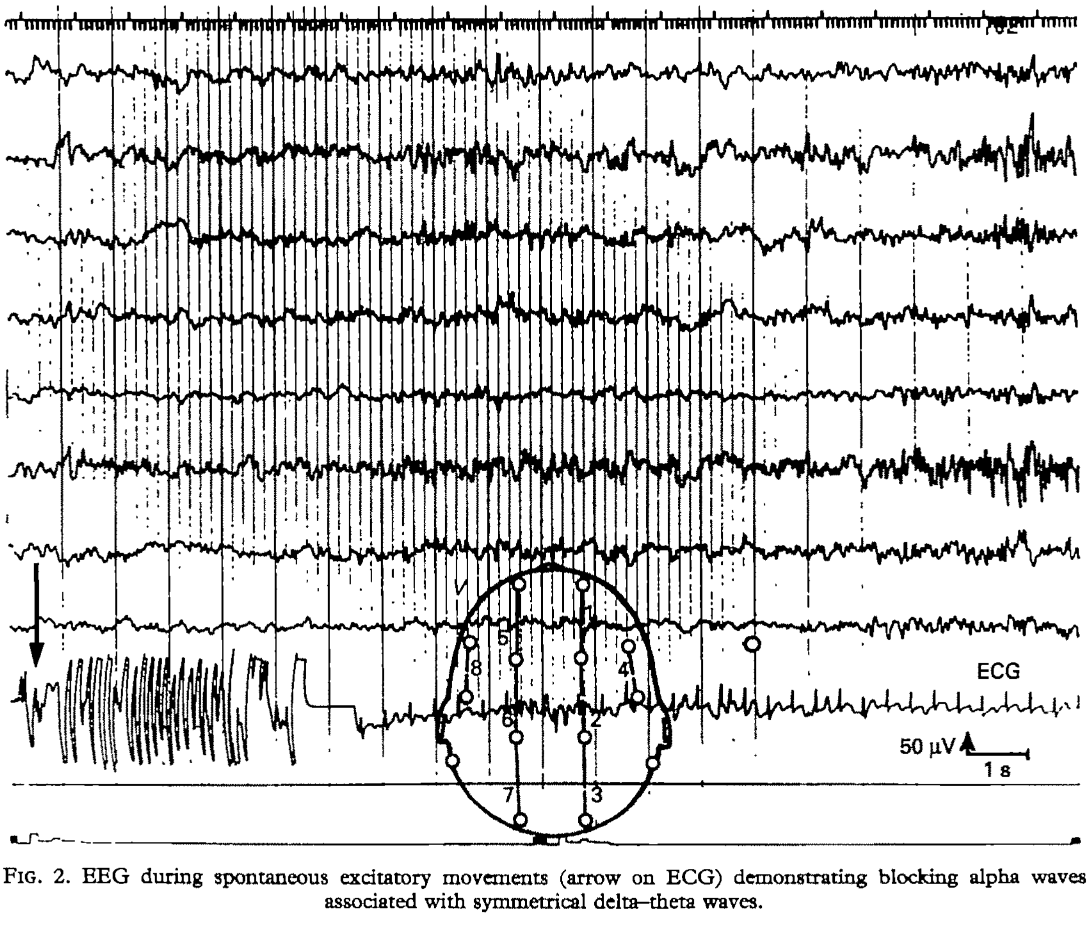


FIG. 2. EEG during spontaneous excitatory movements (arrow on ECG) demonstrating blocking alpha waves associated with symmetrical delta–theta waves.

epileptiform activity. Although there have been several case reports of "seizures" or opisthotonus during recovery from propofol anaesthesia that might have implicated propofol as a convulsant [4–7], careful studies conducted in both animals and humans strongly suggest that, on the contrary, propofol possesses anticonvulsant properties [8–10].

Spontaneous movements occur during induction and recovery from propofol anaesthesia; they have been observed in adults [1, 2] and in children, with a greater incidence in the latter group [3], suggesting an age-dependent differential sensitivity of this phenomenon. We demonstrated recently that, in children, larger induction doses of propofol are associated with a decreasing incidence of spontaneous movements [3]. This child received a large induction dose (5 mg kg^{-1} i.v.—usual dose, 3–4 mg kg^{-1}), thus explaining the lack of spontaneous excitatory movements during the induction phase.

The origin of these movements remains unknown. However, recent evidence suggests involvement of subcortical structures. Indeed, recent studies have demonstrated that subhypnotic doses of propofol possess antiemetic and antipruritic properties [11, 12], which tend to lend support to other subcortical actions of propofol. Interestingly, in these studies the duration of action of propofol was much longer than the hypnotic or cortical durations of action of much greater doses of propofol. This would suggest a much greater sensitivity to propofol of non-cortical structures, compared with cortical areas.

Recently, Kalkman and colleagues showed that propofol 2 mg kg^{-1} i.v. caused significant depression of both electrical and magnetic transcranial motor evoked responses which significantly outlasted any anaesthetic or sedative effects [13]. This marked disparity between the subcortical electrophysiological effects and the apparent (cortical) effects on consciousness is also consistent with significant disparities between the cortical and subcortical pharmacodynamics of propofol. In a study investigating the basic mechanisms associated with excitatory movements caused by propofol anaesthesia, Dolin and colleagues found that excitatory behaviour observed in mice receiving intraperitoneal propofol were augmented by strychnine, a glycine antagonist [14]. Glycine is a ubiquitous amino acid in the central nervous system; however, in its role as an inhibitory neurotransmitter it appears to be confined to subcortical areas [15].

In conclusion, this case report confirms that the spontaneous excitatory movements observed during recovery from anaesthesia with propofol are not associated with cortical epileptic activity and do not differ (nature and origin) from those observed during induction. Although the possibility of true non-cortical seizure activity cannot be excluded, the evidence increasingly points towards other subcortical mechanisms.

REFERENCES

1. Valanne J, Korttila K. Comparison of methohexitone and propofol ("Diprivan") for induction of enflurane anaesthesia in outpatients. *Postgraduate Medical Journal* 1985; **61** (Suppl. 3): 138–143.
2. Fahy LT, Van Mourik GA, Utting JE. A comparison of the induction characteristics of thiopental and propofol. *Anaesthesia* 1985; **40**: 939–944.
3. Borgeat A, Dessibourg C, Popovic V, Meier D, Blanchard M, Schwander D. Propofol and spontaneous movements: an EEG study. *Anesthesiology* 1991; **74**: 24–27.
4. Cameron AE. Opisthotonus again. *Anaesthesia* 1987; **42**: 1124.
5. Hopkins CS. Recurrent opisthotonus associated with anaesthesia. *Anaesthesia* 1988; **43**: 904.
6. Jones GW, Boykett MH, Klok M. Propofol, opisthotonus and epilepsy. *Anaesthesia* 1988; **43**: 905.
7. Collier C, Kelly K. Propofol and convulsions—the evidence mounts. *Anaesthesia and Intensive Care* 1991; **19**: 573–575.
8. Rampton AJ, Griffin RM, Stuart CS, Durcan JJ, Huddy NC, Abbott MA. Comparison of methohexital and propofol for electroconvulsive therapy: effects on hemodynamic responses and seizure duration. *Anesthesiology* 1989; **70**: 412–417.
9. Lowson S, Gent JP, Goodchild CS. Anticonvulsant properties of propofol and thiopentone: Comparison using two tests in laboratory mice. *British Journal of Anaesthesia* 1990; **64**: 59–63.
10. Wood PR, Browne GPR, Pugh S. Propofol infusion for the treatment of status epilepticus. *Lancet* 1988; **1**: 480–481.
11. Borgeat A, Wilder-Smith OHG, Saiah M, Rifat K. Subhypnotic doses of propofol relieve pruritus induced by epidural and intrathecal morphine. *Anesthesiology* 1992; **76**: 510–512.
12. Borgeat A, Wilder-Smith OHG, Saiah M, Rifat K. Subhypnotic doses of propofol possess direct antiemetic properties. *Anesthesia and Analgesia* 1992; **74**: 539–541.
13. Kalkman Cor J, Drummond JC, Ribberink AA, Patel PM, Sano T, Bickford RG. Effects of propofol, etomidate, midazolam and fentanyl on motor evoked responses to transcranial electrical or magnetic simulation in humans. *Anesthesiology* 1992; **76**: 502–509.
14. Dolin SJ, Smith MB, Soar J, Morris PJ. Does glycine antagonism underlie the excitatory effects of methohexitone and propofol? *British Journal of Anaesthesia* 1992; **68**: 523–526.
15. Betz H. Biology and structure of the mammalian glycine receptor. *Trends in Neuroscience* 1987; **10**: 113–117.

British Journal of Anaesthesia 1993; **70**: 462–465

A CONTINUOUS SUBDURAL BLOCK

C. B. COLLIER, S. P. GATT AND S. M. LOCKLEY

SUMMARY

We describe a case of accidental subdural block, after attempted extradural puncture for Caesarean section. Fractionation of the local anaesthetic dose led to avoidance of more serious complications. Subdural fentanyl and a continuous low-dose subdural infusion were used satisfactorily for intra-operative management and postoperative analgesia. As little as 0.5 ml of bupivacaine, hourly, provided satisfactory analgesia over a 15-h period. (Br. J. Anaesth. 1993; **70**: 462–465)

KEY WORDS

Anaesthesia: obstetric. Anaesthetic techniques: extradural, subdural.

Subdural (extra-arachnoid) blocks have been used in the treatment of intractable pain for many years, since the pioneering work by Maher in 1957 [1]. However, the first well-illustrated description of an accidental subdural block, leading to collapse of the patient in the course of a planned extradural block, was that of Boys and Norman in 1975 [2]. Several reports have followed, usually of obstetric patients [3, 4].

There have been few communications on the effects of subdural opioids [5, 6] and none describing satisfactory continuous subdural local anaesthetic block.

CASE REPORT

A 31-yr-old Samoan lady (height 165 cm, weight 77 kg) presented in early labour at 38 weeks gestation, with spontaneous rupture of membranes and an oblique lie. An urgent Caesarean section was planned. The patient had received uneventful extradural blocks for three of her four previous vaginal deliveries and she requested to be awake on this occasion.

18:20. After i.v. infusion of Hartmann's solution 1 litre, the patient was placed in the left lateral position. The extradural space was located easily at the L2–3 level, in the midline, using a 16-gauge Tuohy needle and loss of resistance to air. After negative aspiration for blood or CSF, a dose of 2% lignocaine 4 ml with adrenaline was given through the needle.

18:40. Because of unforeseen circumstances, it was 10 min after the first injection when a test dose of 2% lignocaine 4 ml with adrenaline and fentanyl 40 μg was given through the catheter (after negative aspiration).

18:45. Testing of sensation to pinprick now revealed sensory block to T2. Systolic arterial pressure (SAP) decreased to 70 mm Hg and ephedrine 15 mg was given i.v. over 20 min. This, together with a second 1 litre of Hartmann's Solution restored SAP to 100 mm Hg.

The patient was neither distressed nor drowsy and had no pupillary changes or ventilatory difficulty. Dense motor block in the lower limbs developed over the next few minutes. Fetal cardiotocographic monitoring showed a normal pattern.

19:00. When SAP and sensory level were fairly stable, surgery was commenced.

19:27. A healthy infant was delivered with Apgar scores of 10 and 10, at 1 min and 5 min. The patient had no discomfort during delivery, but at 19:40 she complained of lower abdominal pain during peritoneal closure. This responded to pethidine 20 mg i.v. Attempted aspiration of CSF through the extradural catheter was negative at this time and on several other occasions.

20:15. After completion of surgery (almost 2 h after the block), examination revealed no residual motor or sensory loss and the presence of only mild abdominal discomfort.

20:30. The patient was transferred to the Obstetric Acute Care Unit and an infusion of 0.1% bupivacaine plain was set to run through the "extradural" catheter at 1 ml h^{-1}. Within 1 h, good analgesia was obtained, with sensory block to T12 and minimal motor block.

23:00. The patient remained comfortable, but the sensory block had now risen to T2 and the infusion was stopped. SAP was stable at 100 mm Hg.

02:00. Early the following morning, the patient awoke complaining of pain. The sensory block had regressed to T12. A 1-ml bolus of 0.1% bupivacaine was given, resulting in 2 h of analgesia and sensory block to T4.

C. B. Collier, M.R.C.P., F.R.C.ANAES., F.A.N.Z.C.A.; S. P. Gatt, M.R.C.S., M.D., F.A.N.Z.C.A., F.F.A.INTNSV.CR.; S. M. Lockley, M.B., B.S.; Department of Anaesthesia, Royal Hospital for Women, 188, Oxford Street, Paddington, N.S.W. 2021, Australia. Accepted for Publication: November 4, 1992.

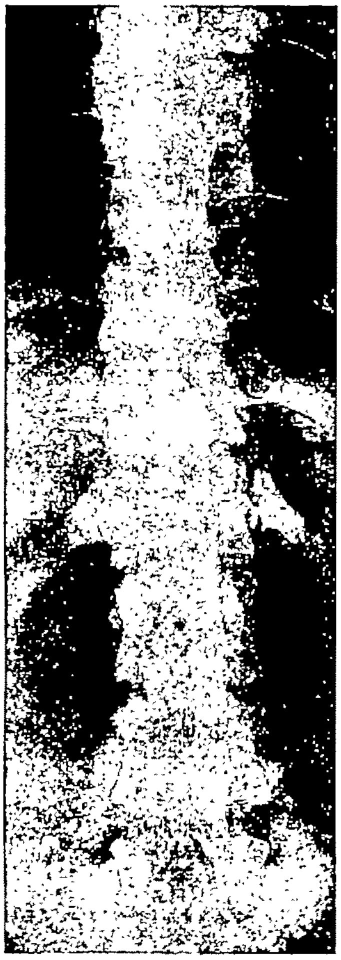


FIG. 1. Antero-posterior radiograph of thoracolumbar spine, showing subdural spread of contrast.

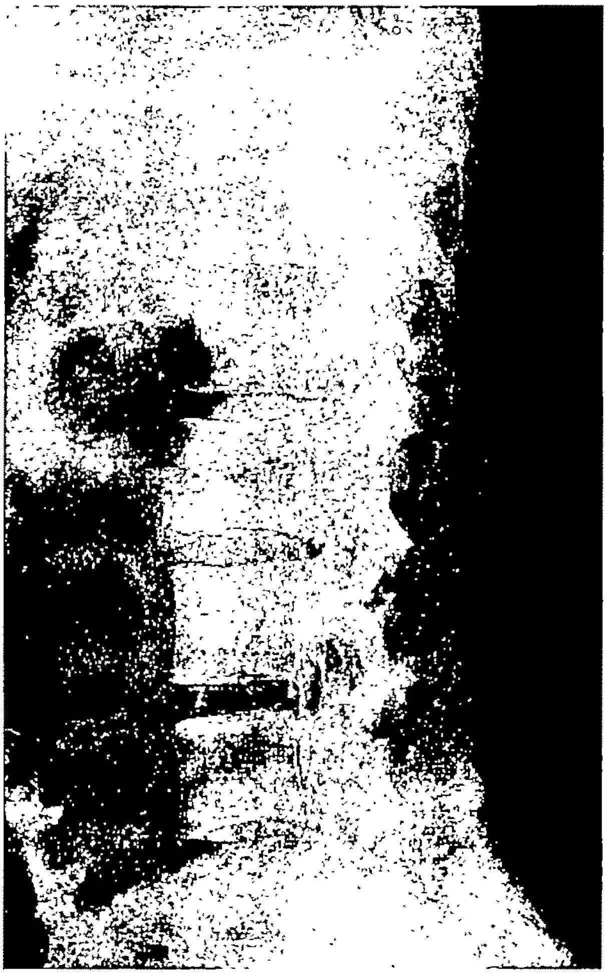


FIG. 2. Lateral radiograph of spine, showing marked ventral and dorsal columns of contrast.

04:00. Three additional boluses of 0.5 ml were given hourly to maintain analgesia. The patient slept well, but was always easily rousable, with only slight heaviness of the legs. As 0.5 ml h^{-1} appeared to be a satisfactory dose, the infusion was restarted at this rate, with good analgesia ensuing.

12:00. The infusion was ceased, a total of 9 ml of bupivacaine having been administered over 15 h. The patient consented to contrast injection and x-ray screening as part of our continuing study of atypical extradural blocks, which are investigated radiographically, after Hospital Ethics Committee approval. In this patient we wished to determine the site of catheter placement, for the clinical pattern could possibly have represented either a pure subdural or subarachnoid block, or a multicompartment block, with the catheter eyes laying in different spaces [7].

Iohexol 240 10 ml was injected and the typical appearances of subdural spread of dye were observed. The antero-posterior view (fig. 1) showed the characteristic "rail-road tracks", from T4 to L4, whilst the lateral view (fig. 2) demonstrated the marked anterior and posterior columns of dye in the subdural space, with "empty" intervertebral foramina. The catheter tip was situated behind the body of the L2 vertebra.

The catheter was withdrawn and inspected, revealing no macroscopic abnormality, and then subjected to the routine testing that we have been performing on all used catheters. First, water was injected down the catheter with observation of the three resulting jets; then the catheter tip was held under water whilst air was injected into the catheter and the streams of bubbles noted. All three eyes were found to be patent, but preferential flow was directed through the proximal eye in both tests. Considerable pressure was required to produce any flow through the middle and distal eyes. Examination with a microscope at 12.5-times magnification revealed a normal proximal eye, but smaller middle and distal eyes, each of approximately 50 % the diameter of the proximal eye.

One hour after the bupivacaine infusion was stopped, sensation had returned to normal, but there was weakness of hip flexion, which resolved 4 h later. The patient made a smooth postoperative recovery, without headache or neurological problems.

DISCUSSION

The cause of this patient's hypotension and high sensory block after an apparently simple extradural block was considered initially to be either subarachnoid or subdural injection. The two conditions may be clinically indistinguishable on some occasions [3, 8]. The relatively slow onset of symptoms and the limited height of the block, together with the inability to aspirate CSF were more suggestive of a subdural block in this patient and radiological screening confirmed the diagnosis.

It appears most likely that this patient's subdural block, which developed 15 min after the 4-ml flushing dose of lignocaine was caused by this initial dose and then compounded by the test dose through the catheter, so that the clinical picture resulted from a total of 8 ml of subdural lignocaine with fentanyl, over a 10-min period. Our usual practice is to give another 6 ml 5 min after the test dose, in the absence of untoward spread, and a further dose a few minutes later, if required, thus "fractionating" the total dose.

If an unwelcome phone-call had not delayed proceedings by 10 min, the 8-ml volume would have been given over a 2–3 min period, followed 5 min later by a bolus of 6 ml. The resulting 14 ml total would almost certainly have produced a high subdural block, perhaps with apnoea and unconsciousness [3]. If "fractionation" had not been used, a bolus of 10–12 ml would have been given, probably producing even more severe symptoms.

Because of the delayed onset of subdural blocks, routine test doses are of only limited value, as it is impractical to wait 15–20 min to exclude this rare complication. However, it may be preferable to use saline for any dose given through the needle, when a continuous block is planned, as the presence of local anaesthetic before catheter insertion usually gives little useful information, except in the case of intravascular injection, and may, indeed, complicate the findings of a subsequent test dose given through the catheter, as happened here.

It is possible that the Tuohy needle was correctly positioned in the extradural space and the catheter perforated the dura on introduction, but as symptoms were noted only 5 min after the first dose through the catheter, it would be highly unlikely that this dose could have initiated the subdural block; more probably, it simply added to the volume already in the subdural space.

The x-ray findings excluded the possibility of a multicompartment block, as did the examination of the catheter after withdrawal, which suggested that only one of the three eyes of the catheter was functioning *in situ*. When the patient's condition had settled after the crystalloid solution and vasopressor agent, and in the presence of good sensory block, it seemed prudent to allow Caesarean section to commence. Other workers have resorted to general anaesthesia [9] or insertion of a second extradural catheter [10] in this situation. Our decision was influenced by the work of Germann, Roberts and Prys-Roberts [11], who demonstrated possible cardiovascular depression produced on combining general anaesthesia with a pre-existing stabilized extradural block. In our situation, the origin of the block was unknown and its stability uncertain; also it has been brought to our attention that several recent cases of maternal mortality and morbidity have involved a combination of general anaesthesia and regional block.

The pattern of the initial subdural block was fairly typical of that after a small dose of local anaesthetic, in that breakthrough pain occurred after 1 h and sensory regression was complete in less than 2 h [3].

The unintentional use of subdural opioids was first documented by Miller, Choi and Chestnut in 1989 [5], when they injected morphine 1 mg into a subdural catheter. This dose produced a 22-h duration of analgesia, with the only side effect being immediate facial flushing which subsided over 10 min. Brown, Atkinson and Standiford, also in 1989 [6], accidentally implanted an extradural catheter in the subdural space of a patient with intractable malignant pain. The catheter was used satisfactorily for morphine administration over a 3-month period, until the patient's demise, at which time he was receiving 12 mg per day.

The use of subdural fentanyl does not appear to have been reported before. A single bolus of 40 µg combined with lignocaine produced only about 1–2 h of analgesia, but there were no obvious side effects.

As many of our postoperative patients receive extradural infusions for analgesia, we continued to use the (presumed) subdural catheter in this patient over a 15-h period, with careful monitoring. A satisfactory dose, producing a fairly constant level of sensory block, with minimal motor block, was found by trial and error to be 0.1% bupivacaine 0.5 ml h^{-1}—less than 10% of our usual extradural dose, and similar to a subarachnoid dose. There appears to be only one previous description of a continuous subdural local anaesthetic infusion [12], and this patient displayed only intermittent sensory block, which may have been partially subarachnoid in origin.

We have demonstrated that it is possible to maintain satisfactory analgesia, safely, with very small doses of local anaesthetic infused into the subdural space. Deliberate subdural block may be a safer technique than continuous subarachnoid block, with its history of neurological problems [13]. However, a recent paper has suggested that neurological damage might result from compression of the spinal cord or nerve roots by a subdural catheter or the injected subdural solution [14], although there appears to be little evidence for this.

REFERENCES

1. Maher RM. Neurone selection in relief of pain: further experiences with intrathecal injections. *Lancet* 1957; **1**: 16–19.
2. Boys JE, Norman PF. Accidental subdural analgesia. A case report, possible clinical implications and relevance to "massive extradurals". *British Journal of Anaesthesia* 1975; **47**: 1111–1113.
3. Collier CB. Accidental subdural block: four more cases and a radiographic review. *Anaesthesia and Intensive Care* 1992; **20**: 215–232.
4. Abouleish E, Goldstein M. Migration of an extradural catheter into the subdural space. A case report. *British Journal of Anaesthesia* 1986; **58**: 1194–1197.
5. Miller DC, Choi WW, Chestnut DH. Subdural injection of local anesthetics and morphine: a complication of attempted epidural anesthesia. *Southern Medical Journal* 1989; **82**: 87–89.
6. Brown G, Atkinson GL, Standiford SB. Subdural administration of opioids. *Anesthesiology* 1989; **71**: 611–613.
7. Beck H, Brassow F, Doehn M, Dziadzka A, Schulte am Esch J. Epidural catheters of the multi-orifice type: dangers and complications. *Acta Anaesthesiologica Scandinavica* 1986; **30**: 549–555.

8. Evans TI. Total spinal anaesthesia. *Anaesthesia and Intensive Care* 1974; **2**: 158–163.
9. Soni N, Holland R. An extensive lumbar epidural block. *Anaesthesia and Intensive Care* 1981; **9**: 150–153.
10. Lee A, Dodd KW. Accidental subdural catheterization. *Anaesthesia* 1986; **41**: 847–849.
11. Germann PAS, Roberts JG, Prys-Roberts C. The combination of general anaesthesia and epidural block. 1: The effects of sequence of induction on haemodynamic variables and blood gas measurements in healthy patients. *Anaesthesia and Intensive Care* 1979; **7**: 229–238.
12. Hartrick CT, Pither CT, Pai U, Raj PP, Tomsick A. Subdural migration of an epidural catheter. *Anesthesia and Analgesia* 1985; **63**: 323–326.
13. Ross BK, Coda B, Heath CH. Local anesthetic distribution in a spinal model: a possible mechanism of neurological injury after continuous spinal anesthesia. *Regional Anesthesia* 1992; **17**: 69–77.
14. McMenemin IM, Sissons GRJ, Brownridge P. Accidental subdural catheterization: radiological evidence of a possible mechanism for spinal cord damage. *British Journal of Anaesthesia* 1992; **69**: 417–419.

British Journal of Anaesthesia 1993; 70: 466–467

POSSIBLE VENOUS AIR EMBOLISM WITH A NEW WATER JET DISSECTOR

J. A. S. SMITH

SUMMARY

An incident of apparent major venous air embolism occurred during hepatic resection using a water jet dissector, an instrument using a high pressure, high velocity jet to disintegrate liver parenchyma. (Br. J. Anaesth. 1993; **70**: 466–467)

KEY WORDS

Complications: venous air embolism. Equipment: water jet dissector. Surgery: hepatic.

CASE REPORT

A 25-yr-old, 59-kg woman presented for left hepatic lobectomy for removal of a single nodule of benign hyperplasia.

General anaesthesia was induced with fentanyl and propofol and muscle relaxation produced with a mixture of pancuronium and vecuronium. Anaesthesia was maintained with nitrous oxide, oxygen and isoflurane at an end-tidal carbon dioxide partial pressure (PE'_{CO_2}) of 4 kPa. The patient was supine with approximately 30° head-up tilt and a sternal retractor was used to provide good exposure for the hepatic resection.

Arterial pressure was monitored invasively from the left radial artery and displayed with ECG, oxygen saturation (Sp_{O_2}) and respired carbon dioxide on a Datex Cardiocap II CG–2GS multifunction monitor coupled to a Sony Model UP-701 videographic printer. Two 16-gauge peripheral venous cannulae were inserted, but in view of the patient's youth and excellent general health a central venous catheter was considered unnecessary.

Progress was uneventful for 80 min, when PE'_{CO_2} decreased by 50% over 3 min while showing an erratic wave pattern suggesting ventilatory effort. Neuromuscular block had been allowed to wane, but the overall depth of anaesthesia and the lack of any extraordinary surgical insult made this change puzzling; nevertheless, further increments of fentanyl and neuromuscular blocker were given. However, before any effect could be expected an abrupt reduction in Sp_{O_2} occurred and the suspicion of venous air embolism raised. The surgeons readily acknowledged this possibility, as their operative field had just filled with froth and bubbles after application of a new water jet dissector. One minute later, both heart rate and arterial pressure decreased markedly, supporting the clinical diagnosis of venous air embolism. There was no change in the ECG trace other than sinus bradycardia.

Nitrous oxide was immediately discontinued and the head-up tilt reversed to increase preload and mitigate against any potential cerebral arterial gas embolism in the event of a patent foramen ovale. These measures halted the downward trend and all variables remained within acceptable limits. Sp_{O_2} and heart rate began to recover within 1 min and PE'_{CO_2} followed soon after (fig. 1). Arterial pressure remained at 85 mm Hg systolic for 5 min but then recovered promptly with removal of a pack that may have been compressing the inferior vena cava. However, the clear change in PE'_{CO_2} before the changes in heart rate and arterial pressure makes caval compression an unlikely event.

A right atrial catheter was contemplated but not inserted, as the incident was resolving before any such action could be undertaken. A precordial Doppler was applied over the right sternal edge within 5 min of the incident, but did not yield any useful information, as cardiac function was normal by this time.

Liver resection was completed uneventfully with

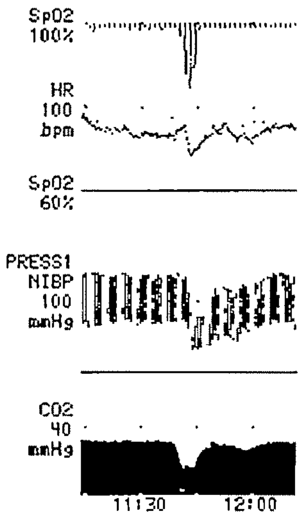


FIG. 1. Videographic printout of the venous air embolism episode as recorded by the Cardiocap monitor.

J. A. S. SMITH, M.B., B.S., F.R.C.ANAES., F.A.N.Z.C.A., Department of Anaesthesia and Intensive Care, Royal Adelaide Hospital, Adelaide, South Australia 5000. Accepted for Publication: October 28, 1992.

the aid of an ultrasonic dissector. Anaesthetic emergence and recovery were uneventful and there was no detectable neurological deficit.

DISCUSSION

The water jet dissector has been developed over the past decade to disintegrate liver parenchyma while sparing the biliary ducts and vascular structures. This allows better recognition and progressive control by diathermy or ligation as appropriate.

The Hepatatom [1–4] is a recent development of this principle, comprising a compressed air pump which forces liquid via a flexible hose through a fine nozzle. The high pressure, high velocity jet stream is designed to increase in diameter with distance from the nozzle tip. It remains coherent for about 30 mm and ends as a fine spray of microdroplets at 40–80 cm, depending on the pressure settings chosen. In use, the tip is advanced from about 40 mm to the point where it cuts liver and then manipulated in a to-and-fro manner as necessary to clear parenchyma. The turbulent interface of water and air at the limits of jet coherence may explain the entry of significant air to an open vein in the resection plane. A Venturi effect within the depths of the wound is another possibility.

The manufacturer's literature indicates that the total volume of fluid used is very small, with no more than 200–300 ml used even in major dissections [1–3]. We can find no mention of venous air embolism in any of the published literature.

While this was the first use of this technique on a patient in our country, it has been used successfully in more than 100 patients in Europe [G. J. Maddern, personal communication]. As this was also the first use of this particular instrument, it is possible that it was not performing to specification, but certainly the variables set were conservative.

In a subsequent laboratory experiment using this same instrument in an aggressive manner on a pig liver, no change in $P\text{E}'_{CO_2}$ could be elicited. However, on directing the jet at biliary structures, the gall bladder was seen to distend markedly with fluid and gas—apparently water and air from the dissector in approximately equal proportions.

While the operative field in surgery such as this lies below the heart and might not ordinarily predispose to venous air embolism, the fact that a turbulent interface of water and air at high pressure is generated by this machine suggests that full monitoring for the detection and treatment of venous air embolism be routine until further human experience clarifies the risk.

ACKNOWLEDGEMENT

I thank Mr G. J. Maddern who provided full details of the development of this jet dissector and invited subsequent attempts to reproduce air embolism.

REFERENCES

1. Bauer HU, Maddern GJ, Blumgart LH. A new water jet dissector—initial experience in hepatic surgery. *British Journal of Surgery* 1991; 78: 502–503.
2. Bauer HU, Maddern GJ, Blumgart LH. Hepatic surgery facilitated by a new jet dissector. *HPB Surgery* 1991; 4: 137–146.
3. Bauer HU, Maddern GJ, Dennison AR, Blumgart LH. Water jet dissection in hepatic surgery. *Minimally Invasive Therapy* 1992; 1: 169–172.
4. Bauer HU, Dennison AR, Maddern GJ, Blumgart LH. Subtotal hepatectomy: a new procedure based on the right hepatic vein. *British Journal of Surgery* 1991; 78: 1221–1222.

British Journal of Anaesthesia 1993; **70**: 468–470

APPARATUS

FRESH GAS REQUIREMENTS OF AN ENCLOSED AFFERENT RESERVOIR BREATHING SYSTEM IN ANAESTHETIZED, SPONTANEOUSLY BREATHING ADULTS

J. R. BARRIE, P. C. W. BEATTY, I. T. CAMPBELL, G. MEAKIN AND T. E. J. HEALY

SUMMARY

Using two methods of determining the onset of rebreathing, we have determined the minimum fresh gas flow rate ($\dot{V}\mathrm{F}$) of the Ohmeda enclosed afferent reservoir breathing system (EAR) in anaesthetized, spontaneously breathing adults. Rebreathing as defined by the Kain and Nunn criteria did not occur when the $\dot{V}\mathrm{F}/\dot{V}\mathrm{E}$ ratio was greater than 0.70. A mathematical model was used to calculate the degree of rebreathing at each $\dot{V}\mathrm{F}$. From this model, rebreathing did not occur when $\dot{V}\mathrm{F}$ was 0.86 $\dot{V}\mathrm{E}$ or more and this value of $\dot{V}\mathrm{F}/\dot{V}\mathrm{E}$ is considered appropriate to eliminate rebreathing in clinical practice. (Br. J. Anaesth. 1993; **70**: 468–470)

KEY WORDS

Anaesthesia: general. Equipment: breathing system, EAR system.

The enclosed afferent breathing system (EAR), developed by Ohmeda, has been demonstrated to be an efficient breathing system for paediatric use during both controlled [1] and spontaneous ventilation [2], and during controlled ventilation in adults [3]. This study was undertaken to determine the minimum fresh gas flow required to prevent rebreathing when the EAR is used during anaesthesia with spontaneously breathing adults. Preliminary work suggests that the efficiency of the EAR is maintained during anaesthesia in relatively young, healthy adults in the supine position [4]. This study aimed to determine the minimum fresh gas requirements for this system when used in elderly patients in the lithotomy position, thus assessing the efficiency of the system under less favourable circumstances found in clinical practice.

APPARATUS

A brief description of the EAR is given below (fig. 1).

A rising bellows, with a capacity of 1500 ml, is incorporated in the inspiratory limb of the system. It is filled from the fresh gas flow and drawn upon during inspiration. A one-way valve is situated in the machine end of the expiratory limb and prevents rebreathing of gas from the expiratory limb during inspiration. Gas passes back on expiration along the inspiratory limb and fills the bellows; thereafter, it spills through the one-way expiratory valve, which has an opening pressure of 1.9 cm H_2O. The system thus functions as a Mapleson A system during spontaneous ventilation.

METHODS

District Ethics Committee approval was obtained and we studied 15 patients aged 64–80 yr, ASA I–III and undergoing elective urological surgery. The patients were not premedicated. Anaesthesia was induced with propofol up to 2.5 mg kg^{-1} and maintained with 66 % nitrous oxide and 2–3 % halothane in oxygen via a laryngeal mask airway. The concentration of halothane was adjusted to obtain adequate anaesthesia and remained constant thereafter. Heart rate, arterial pressure and arterial oxygen saturation (Sp_{O_2}) were monitored non-invasively.

The following measurements were made:

Respiratory flow was measured at the junction between the patient and the breathing system using a heated pneumotachograph (Fleish No. 2). The flow signal from the pneumotachograph was integrated electronically to obtain tidal volume ($V\mathrm{T}$) and expired minute volume ($\dot{V}\mathrm{E}$).

Respiratory gases were sampled continuously from the connector of the laryngeal mask and were analysed for carbon dioxide using an infra-red carbon dioxide analyser (Datex Normocap) to determine end-tidal carbon dioxide partial pressure ($P\mathrm{E'}_{CO_2}$). This sampling resulted in the loss of 150 ml min^{-1} from the system, which was allowed for in subsequent calculations.

All data were recorded on tape (Tandberg Instrumentation Recorder series 100) and analysed via a chart recorder (Grass).

Fresh gas flow ($\dot{V}\mathrm{F}$) was initially set at 100 ml kg^{-1} min^{-1} and the above measurements were made after a 5-min period of stabilization. $\dot{V}\mathrm{F}$ was then reduced by increments of 0.1 × minute volume. Readings were repeated after a 5-min period of

---

J. R. BARRIE, B.SC., M.B., CH.B., F.R.C.ANAES.; P. C. W. BEATTY, M.SC., PH.D., C.ENG. M.B.E.S., F.I.P.S.M.; I. T. CAMPBELL, M.D., F.R.C.ANAES.; T. E. J. HEALY, M.SC., M.D., F.R.C.ANAES.; University of Manchester Department of Anaesthesia, Withington Hospital, Nell Lane, Manchester M20 8LR. G. MEAKIN, M.B., CH.B., F.R.C.ANAES., D.A., Royal Manchester Children's Hospital, Pendlebury, Manchester M27 1HA. Accepted for Publication: October 26, 1992.

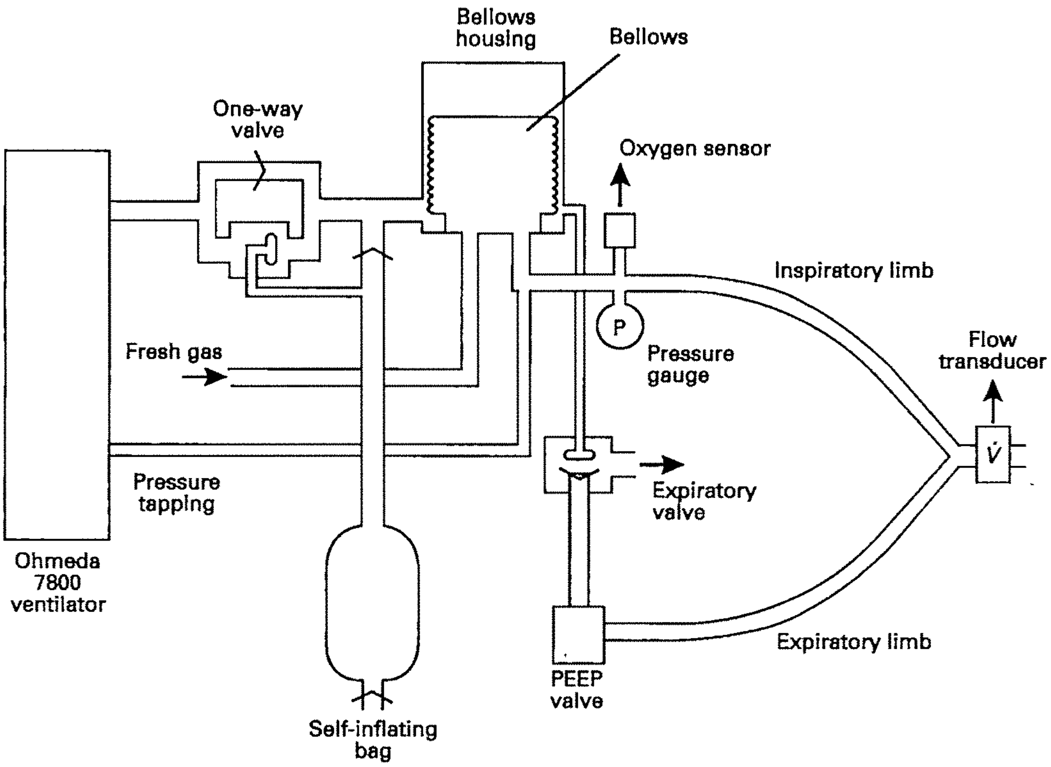


FIG. 1. Diagram of the enclosed afferent reservoir breathing system.

stabilization or when one of the following rebreathing criteria, originally outlined by Kain and Nunn [5], was met:

(i) An increase in $\dot{V}\mathrm{E}$ or tidal volume of 10% or more, not accompanied by a corresponding decrease in $P\mathrm{E}'_{\mathrm{CO_2}}$.

(ii) An increase in $P\mathrm{E}'_{\mathrm{CO_2}}$ of 0.66 kPa or more, which could not be accounted for by a decrease in $\dot{V}\mathrm{E}$.

(iii) An increase in $\dot{V}\mathrm{E}$ of 5% or more, accompanied by an increase in $P\mathrm{E}'_{\mathrm{CO_2}}$ of 0.6 kPa or more.

When the criteria for rebreathing had been met, $\dot{V}\mathrm{F}$ was increased to 100 ml kg^{-1} min^{-1}.

The mathematical model described by Meakin and colleagues [2] was then used to determine the rebreathed volume. Briefly, this assumes that, in the absence of longitudinal mixing of expired gas, rebreathing occurs when $\dot{V}\mathrm{F}$ is less than alveolar ventilation ($V\mathrm{A}$). Thus:

$$V\mathrm{R} = V\mathrm{A} - V\mathrm{F}$$

but

$$V\mathrm{A} = V\mathrm{T} - V\mathrm{D}$$

so

$$V\mathrm{R} = V\mathrm{T} - (V\mathrm{D} + V\mathrm{F})$$

where $V\mathrm{R}$ = volume of rebreathed alveolar gas per breath; $V\mathrm{A}$ = volume of expired alveolar gas per breath; $V\mathrm{F}$ = volume of fresh gas per breath; $V\mathrm{D}$ = apparatus plus anatomical deadspace.

Deadspace—apparatus plus anatomical—was determined by Fowler's method using a custom-written computer program and microcomputer. Flow and capnography signals were aligned at the point of end-expiration by associating the sudden decrease in carbon dioxide concentration with the onset of inspiratory flow [6]. $P\mathrm{E}'_{\mathrm{CO_2}}$ was then plotted against expired volume, giving a sigmoid curve. $V\mathrm{D}$ was the volume expired when the areas above and below this sigmoid portion of the curve were equal. The rebreathed volume calculated above was expressed as a percentage of the tidal volume ($V\mathrm{R}/V\mathrm{T}$%); this was plotted against $\dot{V}\mathrm{F}/\dot{V}\mathrm{E}$.

TABLE I. *Summary of results when Kain and Nunn criteria were met*

Patient no.	$\dot{V}\mathrm{F}$ (ml kg^{-1} min^{-1})	$\dot{V}\mathrm{F}/\dot{V}\mathrm{E}$	$\Delta P\mathrm{E}'_{\mathrm{CO_2}}$ (kPa)	$\Delta\dot{V}\mathrm{E}$ (%)	$V\mathrm{R}/V\mathrm{T}$%
1	72	0.7	0.4	8	5.6
2	53	0.7	1.1	0	4.3
3	50	0.34	0.4	80	6.7
4	59	0.7	1.0	10	35
5	61	0.7	1.3	31	0
6	50	0.5	0.7	18	7.1
7	76	0.65	0.7	30	3.3
8	76	0.6	0.8	66	14
9	65	0.6	0.4	0	2
10	55	0.7	0.2	32	0
11	69	0.4	0.5	79	6

RESULTS

Table I shows the values of $\dot{V}\mathrm{F}/\dot{V}\mathrm{E}$ and $V\mathrm{R}/V\mathrm{T}$%, together with changes in $P\mathrm{E}'_{\mathrm{CO_2}}$ and $\dot{V}\mathrm{E}$, for the values of $\dot{V}\mathrm{F}$ at which rebreathing, according to the Kain and Nunn criteria, were detected. The mean value of $\dot{V}\mathrm{F}/\dot{V}\mathrm{E}$ at which these criteria were fulfilled was 0.60, corresponding to a mean $\dot{V}\mathrm{F}$ of 62.3 ml kg^{-1}. Rebreathing according to the Kain and Nunn criteria was not seen in any patient when $\dot{V}\mathrm{F}/\dot{V}\mathrm{E}$ was > 0.7. Rebreathing was not detected in four patients.

The degree of rebreathing ($V\mathrm{R}/V\mathrm{T}$%) was related inversely to $\dot{V}\mathrm{F}/\dot{V}\mathrm{E}$ (fig. 2). Fitting an arbitrary cubic regression (by Figure Perfect; Biosoft) to the data

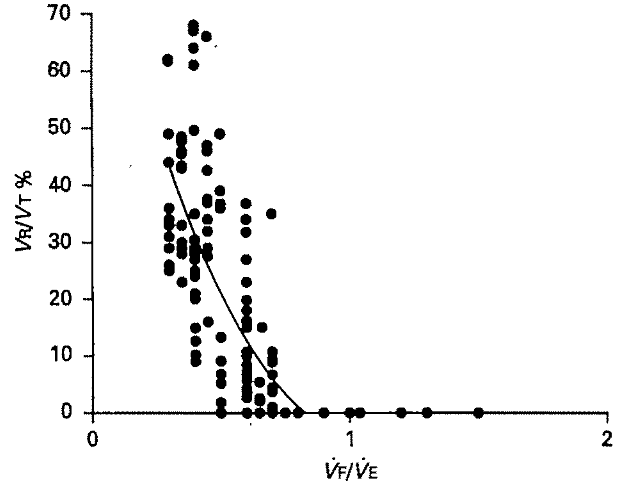


FIG. 2. Plot of the degree of rebreathing (V_R/V_T%) against the ratio of fresh gas flow to minute volume ($\dot{V}_F/\dot{V}_E$).

reveals a take-off point of $\dot{V}_F/\dot{V}_E = 0.86$, this being the value of $\dot{V}_F/\dot{V}_E$ required to eliminate rebreathing completely.

DISCUSSION

Our results indicate that the onset of rebreathing as determined by the Kain and Nunn criteria [5] occurred at mean $\dot{V}_F/\dot{V}_E$ of 0.6 and was not seen at values of $\dot{V}_F$ greater than $0.7\dot{V}_E$. Norman, Adams and Sykes reported that, with the Mapleson A system, the onset of rebreathing occurred when $\dot{V}_F/\dot{V}_E$ was 0.6–0.7 [7], whilst in Alexander's study the onset of rebreathing occurred when $\dot{V}_F/\dot{V}_E$ was 0.76 [8]. Our results are consistent with these studies.

The onset of rebreathing as determined by calculation occurs when $\dot{V}_F/\dot{V}_E$ decreases to less than 0.86. The validity of the derived onset of rebreathing depends on the validity of the assumption that there is little longitudinal mixing of expiratory gas in the delivery tube—an assumption which is fundamental to the explanation of the efficiency of the EAR and the Mapleson A system on which it is based. The $\dot{V}_F/\dot{V}_E$ value of 0.86 is to be compared with the equivalent value (0.78) for the use of the EAR in anaesthetized children breathing spontaneously which was reported by Meakin and colleagues [2] and with data obtained during bench testing of the EAR in which the onset of rebreathing occurred at $0.87\dot{V}_E$ [9].

This method, whilst not suitable for routine monitoring of patients, is useful in that it does not (unlike the Kain and Nunn criteria) rely on a physiological response to rebreathing. It demonstrates rebreathing at an early stage and is of potential value during the assessment of anaesthetic breathing systems in determining values of $\dot{V}_F$ which avoid rebreathing in the clinical situation.

In the present study, the mean $\dot{V}_F$ at which rebreathing occurred as determined by the Kain and Nunn criteria [5], was 62.3 (SEM 2.98) ml kg^{-1}. Unlike controlled ventilation, during which V_T is under the control of the anaesthetist, there is a wide variability in V_T seen in anaesthetized adult patients undergoing surgery whilst breathing spontaneously. This limits the value of recommendations for $\dot{V}_F$ to eliminate rebreathing in terms of ml kg^{-1} min^{-1} and management, as always, has to be guided by the clinical condition of the patient.

In conclusion, the results of this study indicate that the EAR may be used safely in anaesthetized, spontaneously breathing adults with a $\dot{V}_F$ of $0.86\dot{V}_E$ and thus support the view that the EAR may be regarded as a universal anaesthetic breathing system.

ACKNOWLEDGEMENTS

The EAR system was supplied by Ohmeda (BOC Healthcare). The study was supported by a SERC/DTI Teaching Company grant to the University of Manchester Department of Anaesthesia.

REFERENCES

1. Meakin G, Jennings AD, Betty PCW, Healy TEJ. Fresh gas requirements of an enclosed afferent reservoir breathing system during controlled ventilation of children. *British Journal of Anaesthesia* 1992; **68**: 43–47.
2. Meakin G, Jennings AD, Beatty PCW, Healy TEJ. Fresh gas requirements of an enclosed afferent reservoir breathing system in anaesthetized, spontaneously breathing children. *British Journal of Anaesthesia* 1992; **68**: 333–337.
3. Droppert PM, Meakin G, Beatty PCW, Mortimer AJ, Healy TEJ. Efficiency of an enclosed afferent reservoir breathing system during controlled ventilation. *British Journal of Anaesthesia* 1991; **66**: 638–642.
4. Droppert PM, Meakin G, Beatty PCW, Beech M, Shelly MP, Mortimer AJ, Healy TEJ. Fresh gas flow requirements of a new enclosed afferent reservoir breathing system during spontaneous ventilation. *British Journal of Anaesthesia* 1990; **65**: 591P.
5. Kain ML, Nunn JF. Fresh gas economics of the Magill circuit. *Anesthesiology* 1968; **29**: 964–974.
6. Beatty PCW. Measurement of breath-by-breath gas exchange during general anaesthesia using a single pneumotachograph. *Journal of Biomedical Engineering* 1992; **14**: 147–152.
7. Norman J, Adams AP, Sykes MK. Rebreathing with the Magill attachment. *Anaesthesia* 1968; **23**: 75–81.
8. Alexander JP. Clinical comparison of the Bain and Magill anaesthetic systems during spontaneous respiration. *British Journal of Anaesthesia* 1982; **54**: 1031–1036.
9. Jennings AD, Mitchell BC, Beatty PCW, Meakin G, Healy TEJ. The physical characteristics of an Enclosed Afferent Reservoir breathing system. *British Journal of Anaesthesia* 1992; **68**: 625–629.

British Journal of Anaesthesia 1993; 70: 471–473

COMMENTARY

SPINAL EXTRADURAL ABSCESS: PURSUIT OF VIGILANCE

P. R. BROMAGE

SUMMARY

A case of delayed extradural abscess and quadriplegia after extradural steroids is presented. Nine other cases of extradural abscess from the literature are reviewed to illustrate the influence of continuity of hospital admission and informed surveillance on successful outcome when extradural infection arises after extradural medication. A Medic-Alert system is proposed as a means of improving vigilance and neurological outcome for patients at risk. Careful study of the cost-effectiveness of such a scheme is recommended. (Br. J. Anaesth. 1993; **70**: 471–473)

KEY WORDS

Anaesthetic techniques: extradural. Complications: extradural abscess, paralysis. Corticosteroids.

Correspondence columns of the journal have debated the appropriateness of extradural steroids in the management of chronic pain and the danger of extradural abscess and paralysis from immune suppression associated with their use [1–4]. The following case report of extradural abscess after extradural steroids is presented and compared with nine other cases of extradural abscess selected from the recent literature, to illustrate the common factor of vigilance that determines timely treatment and ultimate neurological outcome, regardless of the use of steroids. An early warning system to improve vigilance and outcome is proposed and discussed in terms of feasibility and cost-effectiveness.

CASE REPORT

In the early 1980s, a 61-yr-old woman attended a university-based pain clinic for relief of post-herpetic pain in the upper thorax. After a failed trial of transcutaneous nerve stimulation (TENS), a preliminary extradural injection of 0.5% bupivacaine 5 ml was given at the third thoracic interspace. Segmental analgesia extended from T3 to T8, followed by subjective pain relief for 48 h. Three subsequent extradural injections of 0.5% bupivacaine with methyl prednisolone (Depo-Medrol) 40 mg at 1-week intervals gave excellent relief. All injections were carried out under full aseptic conditions. Surgical face masks were worn and fresh single-dose vials of medications were used on each occasion. The pain returned slowly and, 3 months later, a second course of weekly injections of extradural bupivacaine with methyl prednisolone was given and complete relief obtained.

One week after concluding the second course of injections, the patient undertook a long journey over rough country roads and fell asleep in the back of the car. She awoke with interscapular pain and attributed the pain to muscle strain from the car ride. The pain abated, but returned with increased intensity 3 days later. The next day she was admitted to a local hospital with a diagnosis of "possible facet syndrome" and she was treated by bed rest and pethidine for symptomatic pain relief. Four days after her admission, a consultant neurologist made a tentative diagnosis of extradural abscess. The temperature was slightly increased, to 37.4 °C. Lateral spinal tomograms of the second, third and fourth thoracic vertebrae appeared normal. Expectant treatment continued for a further 2 days. Painful spasms of the arms began on the sixth day after admission. Two days later, and 10 days after admission, a CAT scan and myelogram were performed, revealing a blocked thecal canal in the lower cervical region and quadriplegia developed immediately afterwards. Finally, urgent laminectomy was carried out and the underlying extradural abscess drained, but paralysis persisted.

Table I summarizes the present case and nine other reported cases of extradural abscess associated with extradural analgesia [5–13]. Five arose after extradural steroid injections and four after extradural local anaesthetics without steroids. The incubation period between the assumed date of infection and the appearance of localizing symptoms varied widely, between 4 and 40 days, with a tendency for patients with diabetes or corticoid medication to exhibit the longest intervals. In nine of the 10 patients, the final crescendo sequence of warning signs (increasing pain, neck stiffness, paraesthesiae and root pain) preceded paralysis by an interval of 36–72 h and in one patient (No. 10) by 10 days.

Table II shows the relationship between suspicion of extradural abscess and neurological outcome in the 10 patients reviewed. Absence of awareness of danger was characterized by management at home or in a facility different than the original treating hospital, or by written testimony from the reporting author, as in patient No. 10. A high index of diagnostic suspicion was present with four patients (Nos 3, 4, 8, 9) and all four made a complete recovery. A low level of suspicion appears to have existed with six patients (Nos 1, 2, 5, 6, 7, 10) and all six of these suffered permanent paralysis.

Philip R. Bromage, M.B., B.S., F.R.C.Anaes., F.R.C.P.(C.); Box 1120, R.R.1, Montgomery Center Vermont 05471, U.S.A. Accepted for Publication: September 15, 1992.

TABLE I. *Patient characteristics, extradural injection site and concomitant corticosteroid therapy*

Patient	Age (yr)	Pre-existing pathology	Injection site	Concomitant therapy	Source
1	61	Post herpetic upper thoracic pain	T3–4	Extradural methyl prednisolone 40 mg × 6	Present case
2	56	Low back pain Diabetes, poorly controlled	Lumbar	Extradural triamcinolone	[5]
3	71	Post herpetic thoracic pain	T6–7	Extradural methyl prednisolone 120 mg	[6]
4	20	Reflex sympathetic dystrophy of hand	C6–7	Systemic prednisone 60 mg × 3	[6]
5	65	Low back pain, diabetes	L3–4 L4–5	Extradural methyl prednisolone 80 mg × 3	[7]
6	62	Abdominal aneurysmectomy Rheumatoid arthritis	T9–10	Systemic hydrocortisone 100 mg 6 hourly, 2–3 days	[1]
7	72	Chest trauma	T7–8	—	[8]
8	44	Persistent priapism	L4–5	—	[9]
9	19	Chest trauma	Mid-thoracic	—	[9]
10	52	Repair hiatus hernia Obstructive airway disease	T6–7	—	[10, 11]

TABLE II. *Relationship of outcome to diagnostic signs, location of surveillance and timing of diagnosis and laminectomy. SP = Severe back or neck pain; SN = stiff neck; F = fever; RP = root pain; Ps = paralysis; HC = home care; ADH = admission to different hospital; PDL = prompt diagnosis and laminectomy; EANS = extradural abscess not suspected; DD = delayed diagnosis; LAOP = laminectomy performed after onset of paralysis*

Patient no.	Incubation period (days)	SP	SN	F	RP	Ps	HC	ADH	PDL	EANS	DD	LAOP	Outcome
1	13	+			+	+		+			+	+	Quadriplegia
2	7	+		+				+			+	+	Paraplegia
3	31		+	+					+				Complete recovery
4	40	+			+				+				Complete recovery
5	22	+		+	+	+		+		+	+	+	Paraplegia, death
6	25	+					+			+	+	+	Paraplegia
7	18					+	+	+	+			+	Paraparesis
8	4		+	+					+				Complete recovery
9	4		+						+				Complete recovery
10	9		+	+		+				+	+	+	Residual paralysis

COMMENT

Extradural abscesses have been reported most commonly in the absence of anaesthesia [12–14] and after general anaesthesia [15], after locally invasive procedures such as lumbar puncture [16], spinal anaesthesia [17] or after extradural analgesia, as in the 10 cases reviewed. In one series of 35 abscesses treated aggressively by antibiotics, laminectomy, or both, fever was suppressed and neurological outcome affected adversely by prior administration of systemic steroids [14]. Although there is no statistical evidence to support a cause-and-effect relationship when extradural abscess follows invasive spinal procedures carried out under full aseptic precautions, there is a natural tendency to assume one. While such *post hoc, ergo propter hoc* reasoning may be illogical and groundless, it carries the inherent advantage of heightening awareness among medical attendants and of placing extradural abscess securely on the diagnostic agenda if a spinal procedure is known to have been performed. Signs that might have been given scant attention, especially when attenuated in immune-compromised patients, as in patient No. 1, are noted and given due weight, and the chances of cure by timely diagnosis and definitive treatment are improved.

The crucial clues may not be transmitted or received and correctly interpreted, however. Table II suggests that, while patients under continuous management by the same medical personnel are likely to escape adverse sequelae, because all the information is readily available for early diagnosis and treatment, those admitted to different hospitals may not fare so well. Patient No. 1, although an extreme example, illustrates the common pattern of inadequate information, delayed diagnosis and aimless drift to irrevocable tragedy. The patient had become unaware of a cause-and-effect relationship in the long interval between the extradural steroids and the onset of her new and apparently unrelated pain. Apparently, no history of extradural puncture or immune compromise was available at the hospital of re-admission until too late. In patients Nos 2, 5, 6 and 7, circumstances of discharge and re-admission were less florid, but qualitatively similar, and contributed to lesser degrees of delay, but enough to overrun the brief and final "period of grace" before irreversible neurological damage occurred.

Thus the pattern of events surrounding this review of some published cases seems to indicate a need to improve the follow-up process of patients who may be at risk of extradural abscess after invasive spinal procedures. As verbal informed consent procedures cannot be relied upon to educate patients about the intricacies of remote but catastrophic risks, some mandatory objective warning system is required. This could take the form of a Medic-Alert bracelet

(Medic-Alert Foundation, 12 Bridge Wharf, Caledonian Road, London N1 9UU), stamped with the date and the procedure done and to be worn continuously for 8 weeks after the last intervention.

At first sight such a warning system appears desirable, simple and reasonably cost-effective, but there are hidden expenses that might make it economically unworkable. Inevitably, the heightened sense of danger created by the early warning system will cause false alarms. Each of these is likely to result in re-admission to hospital and full investigation, including bacterial cultures of blood, sputum and urine, together with relevant imaging of the spine. Magnetic resonance imaging (MRI) is the most appropriate, sensitive and least invasive imaging technique currently available, at a present cost of approximately £900 sterling for a full spinal survey. Although MRI is highly sensitive, its specificity is not sufficiently developed to distinguish between blood and pus, for example after an extradural blood patch, and so other sophisticated scanning techniques may be invoked, including labelled leucocyte scans and possibly myelography, bringing the aggregate cost of each false alarm to several thousand pounds sterling. Assuming a 10 % false alarm rate (a not unreasonable estimate in Britain, but an underestimate for litigiously-inclined North America), a national risk load of 10000 patients would require an annual insurance budget of several million pounds to cover the cost of false alarms alone.

A more subtle financial disincentive to an early warning system lies in its medico-legal implications. Regardless of whether or not the system was successful in increasing the standard of care, the very existence of such a mechanism would alert plaintiffs' attorneys to a rich prize in all failures, or alleged failures, to meet the new standard. Physicians involved in any case of neurological sequelae to extradural abscess would be in legal jeopardy on the grounds that the proximate physician abandoned the patient or was negligent in his duty to provide the timely warning that could have prevented permanent damage [18]. As any anticipated salvage gains from timely diagnosis and averted paraplegia is not so easily susceptible to quantification, the net monetary effects of an early warning system cannot be calculated in simple financial terms.

These positive and negative factors need to be studied carefully before implementation of the long-standing view that prescient awareness and early diagnosis are essential to avoid tragic outcome in spinal extradural abscess [15, 16, 19–21]. Analogous problems of cost-effectiveness involving rare but catastrophic anaesthetic events have been faced successfully in other rare conditions, such as malignant hyperthermia and porphyria, and so the profession should be encouraged to apply equal vigour and wisdom in addressing the anaesthetic-related hazards of extradural abscess.

REFERENCES

1. Sowter MC, Burgess NA, Woodsford PV, Lewis MH. Delayed presentation of an extradural abscess complicating thoracic extradural analgesia. *British Journal of Anaesthesia* 1992; **68**: 103–105.
2. McQuay HJ, Jadad AR. Is steroid therapy a contraindication to extradural analgesia. *British Journal of Anaesthesia* 1992; **68**: 540–541.
3. Burn JMB, Langdon L. Duration of action of methyl prednisolone. A study in patients with the lumbosciatic syndrome. *American Journal of Physical Medicine* 1974; **53**: 29–34.
4. Jacobs S, Pullan PT, Potter JM, Shenfield GM. Adrenal suppression following extradural steroids. *Anaesthesia* 1983; **38**: 953–956.
5. Chan S-Z, Leung S. Spinal epidural abscess following steroid injection for sciatica. *Spine* 1989; **14**: 106–108.
6. Strong WE. Epidural abscess associated with epidural catheterization: A rare event? Report of two cases with markedly delayed presentation. *Anesthesiology* 1991; **74**: 943–946.
7. Goucke CR, Graziotti P. Extradural abscess following local anaesthetic and steroid injection for chronic low back pain. *British Journal of Anaesthesia* 1990; **65**: 427–429.
8. McDonogh AJ, Cranney BS. Delayed presentation of an epidural abscess. *Anaesthesia and Intensive Care* 1984; **12**: 364–365.
9. North JB, Brophy BP. Epidural abscess: a hazard of spinal epidural anaesthesia. *Australia and New Zealand Journal of Surgery* 1979; **49**: 484–485.
10. Ferguson JF, Kirsch WM. Epidural empyema following thoracic epidural block. *Journal of Neurosurgery* 1974; **41**: 762–764.
11. Saady A. Epidural abscess complicating thoracic epidural analgesia. *Anesthesiology* 1976; **44**: 244–246.
12. Male CG, Martin R. Puerperal epidural abscess. *Lancet* 1973; **1**: 608–609.
13. Baker AS, Ojemann RG, Swartz MN, Richardson EP. Spinal epidural abscess. *New England Journal of Medicine* 1975; **293**: 463–468.
14. Danner RL, Hartman BJ. Update of spinal epidural abscess: 35 cases and review of the literature. *Reviews of Infectious Diseases* 1987; **9**: 265–274.
15. Schreiner EJ, Lipson SF, Bromage PR, Camporesi EM. Neurological complications following general anaesthesia. *Anaesthesia* 1983; **38**: 226–229.
16. Bergman I, Wald ER, Meyer JD, Painter MJ. Epidural abscess and vertebral osteomyelitis following serial lumbar puncture. *Pediatrics* 1983; **72**: 476–480.
17. Loarie DJ, Fairley HB. Epidural abscess following spinal anesthesia. *Anesthesia and Analgesia* 1978; **57**: 351–353.
18. Toth RS. Medical malpractice: physician as a defendant. In: Hirsch HL and American College of Legal Medicine, eds. *Legal Medicine: Legal Dynamics of Medical Encounters.* St Louis: The C. V. Mosby Company, 1988; 482–487.
19. Hulme A, Dott NM. Spinal epidural abscess. *British Medical Journal* 1954; **1**: 64–68.
20. Hancock DO. A study of 49 patients with acute spinal extradural abscess. *Paraplegia* 1973; **10**: 285–288.
21. Russell NA, Vaughan R, Morley TP. Spinal epidural infection. *Canadian Journal of Neurological Sciences* 1979; **6**: 325–328.

British Journal of Anaesthesia 1993; **70**: 474P–488P

ABSTRACTS

PROCEEDINGS OF THE ANAESTHETIC RESEARCH SOCIETY

LONDON MEETING

NOVEMBER 20–21, 1992

(The name of the author presenting the paper is shown in bold type. * Indicates non-member.)

All authors have certified that, where appropriate, studies have been conducted with the approval of the relevant Human Ethics Committee or Animal Experiment Review Committee.

COMPARISON OF SPONTANEOUS SIGHS AND MANUAL INFLATIONS IN ANAESTHETIZED PATIENTS BREATHING AIR AND OXYGEN

A. C. DOW* AND N. W. GOODMAN
University Department of Anaesthesia, Southmead Hospital, Bristol

The breaths after a sigh, or augmented breath [1], have a smaller tidal volume and shorter inspiratory time than the breaths preceding it [2]. We have investigated some of the factors that cause these changes. We compared natural sighs, which we term "active sighs", with manual inflations ("passive sighs") in patients breathing air and hyperoxic mixtures of either 33% oxygen in nitrous oxide or 100% oxygen.

Patients of slim build and with easily manageable airways were included in the study. We studied 19 ASA I patients (16 women), aged 23–52 yr and weighing 49–83 kg. Patients were premedicated with a benzodiazepine if desired ($n = 9$).

Patients were monitored by pulse oximetry. Anaesthesia was induced with propofol and a laryngeal mask was inserted. Anaesthesia was maintained by a three-step reducing infusion of propofol stepped at 10-min intervals but the interval was prolonged if patients were clinically lightly anaesthetized. Patients started by breathing air and later breathed a hyperoxic mixture, from a Mapleson A system with flows of at least 10 litre min^{-1}. If patients sighed, we attempted to administer a matching passive sigh of the same tidal volume; otherwise we aimed for a passive sigh approximately 2.5 times the average tidal volume. Ventilatory variables were measured by inductance plethysmography. Continuous output from a capnograph was recorded.

The 10 breaths preceding and 20 breaths succeeding sighs were analysed in groups of five breaths, normalized for each sigh to a baseline taken as the mean of the group of five breaths before the sigh. Statistical comparisons were made on the first group of five after the sigh.

We analysed 33 active sighs, averaging 270% of baseline, and 37 passive sighs (262% of baseline). Tidal volume was reduced by an active sigh (95% confidence intervals of means 88–97% of baseline) or a passive sigh (89–95%). Sighs when breathing air had more effect than sighs during hyperoxia: with 100% oxygen, for active sighs the difference was 14% (3–25%); for passive sighs 10% (3–17%). There were no differences as a result of nitrous oxide. Active sighs shortened inspiratory time to 92% (90–94%), passive sighs to 98% (96–99%); we could not distinguish any effect of gas mixture.

We conclude that part of the decrease in tidal volume after a sigh is caused by transient chemical changes. The shortening of inspiratory time is either programmed in the respiratory centre when the sigh is generated, or caused by mechanoreceptor input not mimicked by manual inflation.

REFERENCES

1. Glogowska M, Richardson PS, Widdicombe JG, Winning AJ. *Respiration Physiology* 1972; **16**: 179–196.
2. Goodman NW, Kestin IG. *British Journal of Anaesthesia* 1992; **68**: 48–53.

HYPERBARIC DECOMPRESSION BUBBLE FORMATION—BUILDING ON THE MAPLESON MODEL OF GAS DYNAMICS

V. FLOOK, O. EFTEDAL AND A. O. BRUBAKK
Department of Biomedical Sciences, University of Aberdeen, Aberdeen, Sintef Unimed, Trondheim and Department of Biomedical Engineering, University of Trondheim, Trondheim, Norway

In recent years the aim of those concerned with performing safe decompressions has changed from symptom-free decompressions to bubble-free decompressions, as evidence increases that symptomless dives can produce bubbles and bubbles may cause long-term damage to health. The basis for bubble formation is the partial pressure of inert gas in tissues and blood. The Mapleson model of inert gas uptake [1] provides an ideal means of calculating gas partial pressures during both uptake and washout of inert gas during diving and subsequent decompressions.

To this basic model has been added the concept of "inherent unsaturation". This means that as oxygen partial pressure decreases to less than arterial levels, bubble formation is prevented because the total pressure of dissolved gases is less than environmental pressure, unless the tissue is supersaturated with inert gas. Total gas content is calculated for tissue in equilibrium with venous blood throughout the decompression.

It is assumed that when there is sufficient gas to form a bubble, bubbles have formed. A simplistic model of bubble dynamics is used to plot the change in size of the bubbles from inception until they are finally resolved.

We compared the results from the model with pulmonary artery bubble counts in pigs using transoesophageal ultrasonic scanning

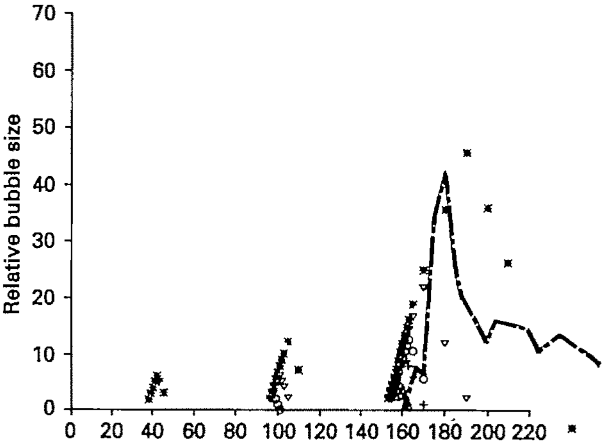


FIG. 1. Bubble count (broken line) compared with relative bubble size in the five fastest compartments of the Mapleson model: time constants 0.86 (△); 1.97 (+); 3.1 (○); 5.3 (▽); and 12.3 (✱).

and early results indicate that the model predicts considerable bubble growth for the decompression profiles in which many bubbles were detected. Figure 1 compares bubble count with predicted bubble size in the five fastest compartments of the Mapleson model. We do not yet know what the relative bubble size means in terms of real physical size, neither do we know the origin of bubbles which are detected in the pulmonary artery. This combined theoretical and experimental approach, together with inert gas quantification techniques developed by Mapleson's team in the early 1960s, should provide much needed information about the formation of bubbles during decompression.

REFERENCE

1. Mapleson WW. *Journal of Applied Physiology* 1963; **18**: 197–204.

EFFECT OF THREE DIFFERENT SURGICAL PRONE POSITIONS ON LUNG VOLUMES IN HEALTHY, AWAKE VOLUNTEERS

N. HENNESSY*, R. P. MAHAJAN* AND
A. R. AITKENHEAD
University Department of Anaesthesia, Queen's Medical Centre, Nottingham

Anaesthetists have long recognized that the prone position for surgery can cause respiratory embarrassment. Surgeons vary in their choice of prone position. The different prone positions demanded by surgeons may result in varying degrees of change in lung volume.

Three different prone positions used commonly by surgeons for back surgery were studied in 10 healthy volunteers (eight males) with a mean age of 31.1 yr (range 26–36 yr), mean weight of 69.4 kg (range 52–84 kg) and mean height of 1.73 m (range 1.6–1.8 m). Each volunteer was placed in the optimal operating position, in the same order, by the same surgeon according to his normal practice. The three positions were: (1) using two padded supports for the thorax and pelvis with the abdomen free; (2) using a preformed laminectomy support (Eschmann); (3) the knee–chest position.

The prone position without support was used as a baseline control. Lung volumes using helium dilution were calculated for each awake volunteer in each position. These were: functional residual capacity (FRC), residual volume (RV), expiratory reserve volume (ERV), inspiratory capacity (IC), slow vital capacity (SVC) and total lung capacity (TLC).

TABLE I. *Mean* (SD) *values for lung volumes in the four different prone positions*

	Two supports	Frame	Knee–chest	Control
FRC	2.85 (0.66)	3.15 (0.77)	3.83 (0.87)	2.77 (0.79)
RV	1.45 (0.47)	1.63 (0.49)	1.94 (0.48)	1.56 (0.48)
ERV	1.39 (0.14)	1.51 (0.14)	1.88 (0.22)	1.21 (0.16)
IC	3.40 (0.65)	3.40 (0.74)	3.01 (0.71)	3.59 (0.59)
TLC	6.25 (1.05)	6.51 (0.97)	6.84 (1.06)	6.36 (1.06)
SVC	4.78 (0.73)	4.88 (0.70)	4.89 (0.75)	4.80 (0.77)

The greatest increase in lung volumes was associated with the use of the knee–chest position (table I). Changes in FRC ($P < 0.001$), ERC ($P < 0.01$), RV ($P < 0.05$) and TLC ($P < 0.05$) were significant. Both FRC ($P < 0.01$) and ERV ($P < 0.05$) increased significantly in the frame position. No advantage was gained in comparison to the control position when two supports were used for the thorax and pelvis, and lung volumes were not significantly different from control values. We conclude that of these three prone positions in awake volunteers, the knee–chest position causes least respiratory restriction.

EFFECT OF SELECTIVE CELL SEPARATION ON RESPIRATORY FUNCTION AFTER AORTIC ANEURYSM SURGERY

M. McKAVNEY, R. J. CORSON, A. HANBURY,
A. J. MORTIMER, M. KEEGAN, C. N. McCOLLUM AND
I. T. CAMPBELL
University Departments of Anaesthesia and Surgery, Withington Hospital, Manchester

Hypoxaemia after abdominal surgery is caused by reduction in lung volume secondary to abdominal pain [1] but is also associated with platelet aggregation in peripheral veins and pulmonary embolization [2]. The effect of selective haemodilution on ventilatory function one week after elective aortic aneurysm surgery was investigated.

Twenty-two patients for aortobifemoral graft were randomized for selective haemodilution ($n = 11$) or normal treatment ($n = 11$). Selective haemodilution before operation removed 30% of circulating platelets, 15% of circulating granulocytes and decreased the concentration of haemoglobin by 2.3 g/dl. Cells were stored at room temperature and reinfused on wound closure. Volume was replaced with Gelofusine. Arterial $P\text{O}_2$, $P\text{a}_{\text{CO}_2}$, alveolar–arterial gradients ($P\text{A}_{\text{O}_2} - P\text{a}_{\text{O}_2}$) and lung volumes were measured before operation and nominally six days after operation. Several patients treated normally were not well enough on day 6 and were measured 6–9 (median 7) days after operation. Of the patients receiving haemodilution, 10 patients were studied 6, and one patient 7 days after operation ($P < 0.05$).

In the patients receiving haemodilution, $P\text{a}_{\text{O}_2}$ before operation was mean 11.9 (SD 1.6) kPa and in the controls 12.0 (1.5) kPa: $P\text{a}_{\text{CO}_2}$ was 5.3 (0.5) kPa and 5.4 (0.5) kPa, respectively. There was no difference in lung volume. After operation, in the cell-separated group, $P\text{a}_{\text{CO}_2}$ decreased by mean 0.25 (SEM 0.07), $P\text{a}_{\text{O}_2}$ by 1.1 (0.36) and ($P\text{A}_{\text{O}_2} - P\text{a}_{\text{O}_2}$) increased by 0.33 (0.36) kPa, compared with the controls where $P\text{a}_{\text{CO}_2}$ decreased by 0.59 (0.16) kPa ($P < 0.1$ compared with cell-separated group), $P\text{a}_{\text{O}_2}$ by 1.9 (0.6) kPa ($P < 0.1$) and ($P\text{A}_{\text{O}_2} - P\text{a}_{\text{O}_2}$) increased by 2.1 (0.48) kPa ($P < 0.005$ compared with the cell-separated group). Total lung and functional residual capacities decreased by between 13 and 20% in both groups but there were no differences between the groups.

REFERENCES

1. Craig DB. *Anesthesia and Analgesia* 1981; **60**: 46–52.
2. McCollum CN, Campbell IT. *British Journal of Surgery* 1979; **66**: 703–709.

EFFECTS OF MORPHINE AND ITS METABOLITES ON OPIATE RECEPTOR BINDING AND CYCLIC ADENOSINE-3′,5′-MONOPHOSPHATE (cAMP) FORMATION IN HUMAN NEUROBLASTOMA CELLS

D. G. LAMBERT AND R. A. HIRST
University Department of Anaesthesia, Leicester Royal Infirmary

The biochemical effects of opioid receptor occupancy are well established and include hyperpolarization, inhibition of depolarization-induced calcium entry and inhibition of formation of the second messenger, cAMP [1]. We have investigated the effects of morphine and its metabolites (morphine-6-glucuronide (M6G) and morphine-3-glucuronide (M3G)) in comparison with fentanyl on opioid receptor binding and cAMP formation in intact SH-SY5Y neuroblastoma cells.

Opioid receptor binding was assessed using the non-selective opiate ligand [^{3}H]diprenorphine. Affinity (K_{50}) values were computed as described previously [2]. For cAMP accumulation, cells were incubated with the phosphodiesterase inhibitor IBMX, opioids and forskolin (to increase cAMP) for 15 min. cAMP was assayed by a radioreceptor method as described previously [3]. Data are presented as maximum and half-maximum (IC_{50}) percent inhibition of forskolin-stimulated cAMP formation.

Both morphine and fentanyl were equipotent in the receptor binding assay, but fentanyl was approximately seven-fold more potent than morphine in inhibiting cAMP formation, and was approximately twice as efficacious as morphine. M6G was approximately four-fold weaker than morphine in the receptor binding assay but was equipotent with morphine in inhibiting

TABLE II. *Mean* (SEM) *biochemical effects of morphine, morphine-6-glucuronide* (*M6G*), *morphine-3-glucuronide* (*M3G*) *and fentanyl* (n = 5–8). *Significant differences,* $P < 0.05$, *compared with:* * *morphine or fentanyl;* † *morphine or M6G*

Drug	K_{50} (nmol litre^{-1})	IC$_{50}$ cAMP (nmol litre^{-1})	Max. inhibition cAMP (%)
Morphine	96 (10)	193 (58)	29 (4)
M6G	393 (96)*	113 (40)	29 (3)
M3G	> 30000	> 30000	—
Fentanyl	99 (5)	27 (8)†	56 (5)†

cAMP formation: M3G was ineffective (table II). These data suggest that the different therapeutic profiles of morphine, M6G and fentanyl may involve changes in neuronal cAMP formation and subsequent cAMP-dependent protein phosphorylation.

ACKNOWLEDGEMENT

Supported in part by the University of Leicester Research Fund.

REFERENCES

1. Childers SR. *Biochemical Pharmacology* 1991; **48**: 1991–2003.
2. Cheng YC, Prusoff WH. *Biochemical Pharmacology* 1973; **22**: 3099–3108.
3. Brown L, Albano JDM, Ekins RP, Sgherzi AM. *Biochemical Journal* 1971; **121**: 561–562.

EFFECT OF PROPOFOL ON NEUTROPHIL RESPIRATORY BURST

A. J. OGILVY*, S. M. WHITELEY*, M. J. KOWOLIK AND P. G. MURPHY

Department of Anaesthesia, Leeds General Infirmary

A major mechanism by which neutrophils destroy bacteria is via generation of reactive oxygen species, a process known as respiratory burst [1]. Thiopentone, Althesin and most inhalation anaesthetic agents interfere with this mechanism [2]. In this *in vitro* study we have examined the effect of propofol on this aspect of neutrophil function.

Neutrophil suspensions were harvested from blood donated by 15 healthy and 15 critically ill adults, and incubated with propofol 12.5, 25 or 50 μmol litre^{-1} or Intralipid as control. The respiratory burst was induced by adding the neutrophil stimulant N-formyl-L-methionyl-L-leucyl-L-phenylalanine (FMLP 10 μmol litre^{-1}) and measured using luminol-enhanced chemoluminescence. This was quantified as an integral of its intensity with time (mV s) and the results analysed using repeated-measures ANOVA. Individual groups were compared using a paired *t* test to which a Bonferoni correction was applied, and 95% confidence intervals for the differences between the means (95% CI).

Table III shows the concentration-dependent attenuation of FMLP-induced chemoluminescence by propofol. This was observed in the neutrophils prepared from both patients and healthy volunteers, although the baseline activity was significantly greater in the patient group ($P = 0.0002$, Mann–Whitney *U* test, 95% CI of difference between medians 6322–37639). We conclude that, *in vitro*, propofol interferes with the neutrophil respiratory burst.

TABLE III. *Mean* (SEM *and 95% confidence intervals* (*CI*)) *FMLP-induced chemoluminescence* (*mV s*) *in neutrophil suspensions incubated with propofol or Intralipid.* *** $P < 0.001$ *compared with Intralipid* (*ANOVA*)

		Propofol (μmol litre^{-1})		
	Intralipid	12.5	25	50
Controls	11396 (1312)	8021 (957)***	6495 (810)***	4835 (517)***
95% CI with Intralipid		2244–4506	3567–6234	4645 (8477)
Patients	39983 (8305)	29805 (7612)***	25010 (6398)***	18102 (4872)***
95% CI with Intralipid		6360–13996	10064–19882	13878–29885

ACKNOWLEDGEMENT

The authors are grateful to ICI Pharmaceuticals for financial support.

REFERENCES

1. Babior BM. *New England Journal of Medicine* 1978; **298**: 659–668.
2. Stevenson GW, Hall SC, Rudnick S, Seleny FL, Stevenson CH. *Anesthesiology* 1990; **72**: 542–552.

CLONAL VARIATION IN RESPONSE TO ENFLURANE ANAESTHESIA WITH *DAPHNIA MAGNA*

A. P. MYLES*, P. CALOW* AND C. S. REILLY

Departments of Anaesthesia and Animal and Plant Sciences, University of Sheffield

A previous study has shown that the freshwater invertebrate *Daphnia magna* may be used as a model of the potency of inhalation anaesthetics [1]. We have since used *D. magna* to investigate several aspects which affect anaesthetic potency. Previous workers have used selective breeding of both mice and nematode worms based on their sensitivity to anaesthesia in an attempt to characterize anaesthetic sites of action [2, 3]. Daphnids reproduce by parthenogenesis producing clones. Genetic differences in response to a number of toxicants have been observed previously between clones of *D. magna*. In this study we have investigated the interclonal variation in the sensitivity to enflurane.

Three clones (F, C, PS-1), known to be genetically distinct, were used in the study. All animals were cultured under standard conditions at 20 °C and 2–6-week-old individuals were used. Standard anaesthetic flowmeters and Cyprane vaporizers delivered the enflurane in oxygen (1 litre min^{-1}). Enflurane concentrations were measured using a Datex Normac. The anaesthetic mixture flowed into two glass observation chambers through two aquarium pumps. The gas was bubbled through 200 ml of the same analytical grade water in which the animals were cultured. The chambers were enclosed in a glass water bath and maintained at a constant temperature of 20 °C. The bath was raised so the base of the observation chambers was clearly visible. The enflurane concentration was increased by increments of 0.1% and the animals were allowed to equilibrate for 1 h at each step.

TABLE IV. *Mean* (*95% confidence intervals*) EC_{50} *values for response to enflurane for the three clones at different ages*

	Age (weeks)		
Clone	2	4	6
F	1.067 (1.02–1.12)	1.631 (1.56–1.7)	1.575 (1.39–1.78)
C	1.116 (1.12–1.21)	1.587 (1.51–1.66)	1.382 (1.29–1.48)
PS-1	1.162 (1.09–1.23)	1.245 (1.18–1.32)	1.373 (1.31–1.44)

Anaesthesia was defined as lack of limb movement in response to a noxious stimulus (cold strong light source). The number responding to the stimulus at each concentration was recorded. Concentration–response curves and EC_{50} values were calculated from the results using the PC Pharm computer program (table IV).

Genetic differences in response to enflurane were observed. Clonal differences in response could be manipulated to provide a model which may be of use in studies of mechanisms of anaesthesia.

REFERENCES

1. McKenzie JD, Calow P, Nimmo WS. *British Journal of Anaesthesia* 1989; **63**: 489–491.
2. Koblin DD, Deady JE, Eger EI. *Anesthesiology* 1982; **56**: 18–24.
3. Morgan PG, Cascorbi HF. *Anesthesiology* 1988; **62**: 738–744.

MEMBRANE ACTION OF VOLATILE ANAESTHETICS: EFFECT OF HALOTHANE ON MICROVISCOSITY

B. APPADU, D. J. ROWBOTHAM, R. GRIFFITHS, S. GRAHAM AND R. I. NORMAN
University Department of Anaesthesia, Leicester Royal Infirmary

Volatile anaesthetic agents have been shown to increase cell membrane fluidity [1]. However, the precise site of this change is unknown. We have studied the effects of halothane on microviscosity at specific sites within cell membranes.

Erythrocyte ghost membranes were prepared from the blood of 10 healthy volunteers by the method described by Niggli and colleagues [2] and stored at −70 °C. A series of n-(9-anthroyloxy) fatty acid probes were used to measure microviscosity [3]. Ghost membranes were equilibrated at 37 °C with air and 0.5%–4.0% halothane via a calibrated Fluotec 3 vaporizer for 15 min. Probes were then added to the membrane suspension and incubated for 30 min before measurement of fluorescence polarization by a Perkin–Elmer LS50 luminescence spectrometer.

Figure 2 shows the reduction in mean polarization intensity ($n = 10$) for each probe with increasing concentrations of halothane ($P < 0.01$, repeated measures MANOVA for paired data).

Halothane causes a dose-dependent decrease in membrane microviscosity throughout the lipid bilayer of erythrocyte ghost membranes. This change in microviscosity does not saturate within the range of clinical concentration of halothane. The generalized action of halothane on membrane dynamics may underlie functional changes in cellular membranes during anaesthesia.

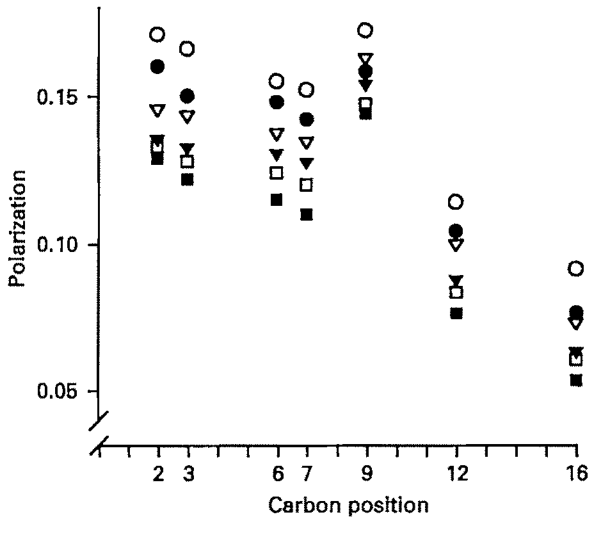


FIG. 2. Reduction in mean polarization intensity for each probe with air (○) and 0.5% (●), 1% (▽), 2% (▼), 3% (□), 4% (■) halothane.

REFERENCES

1. Mastrangelo CJ, Trudell JR, Edmunds HN, Cohen EN. *Molecular Pharmacology* 1978; **14**: 463–467.
2. Niggli V, Adurgah ES, Penniston JT, Carafoli E. *Journal of Biological Chemistry* 1980; **256**: 395–400.
3. Thurlborn KR, Tilley LM, Sawyer WH, Treloar FE. *Biochimica et Biophysica Acta* 1979; **559**: 166–178.

ULTRASOUND MEASUREMENT OF MUSCLE THICKNESS IN THE ESTIMATION OF FAT FREE MASS

T. WATT, B. FARAGHER, D. J. WITHERS, R. E. ENGLAND, D. F. MARTIN AND I. T. CAMPBELL
Department of Anaesthesia, University of Manchester, Withington Hospital, Manchester

It is normal practice to regard the body as a two-compartment model—fat and fat free mass. Conventional techniques of assessing body mass [1] and composition rely either on complex apparatus, the administration of radioactive isotopes, or both, or they make assumptions which, in the critically ill patient retaining large amounts of fluid, are not valid. If the efficiency of nutritional support in multiple organ failure is to be evaluated, a technique of monitoring changes in fat free mass is needed which works in the presence of abnormal fluid retention.

The evidence is that in multiple organ failure, fluid is retained in subcutaneous and visceral tissue and not in the body of the muscle [2]. We have shown previously in 30 normal volunteers, a strong correlation ($r = 0.959$) between fat free mass (calculated from body weight and skinfold thickness) and total muscle thickness measured using ultrasound over six sites: the anterior thigh, forearm, biceps, triceps, rectus abdominus and the calf [3]. This compared favourably with the more conventional indices of lean body mass such as mid-upper arm circumference (0.789), arm muscle area (0.850) and arm muscle circumference (0.841).

Data on 70 normal volunteers has now been analysed, using linear multiple regression analysis, to determine what sites accounted for most of the variation. The correlation coefficient of fat free mass and total muscle thickness measured over biceps, thigh and forearm was 0.870. Adding height increased r to 0.922. For biceps and height alone, r was 0.919. The 95% confidence interval for the difference between the "true" and computed fat free mass was ±19.7%. These figures compare with r values for the same group of 0.737 for mid-upper arm circumference, 0.852 for arm muscle circumference and 0.854 for arm muscle area.

Measurement of total muscle thickness over biceps, front of thigh and forearm may provide a method of monitoring changes in body mass and composition as effective as measurements of arm circumference.

REFERENCES

1. Shizgal HM. *Surgical Clinics of North America* 1981; **61**: 729–741.
2. Helliwell TR, Coakley JH, Wagenmakers AJM, Griffiths RD, Campbell IT, Green CJ, McClelland P, Bone JM. *Journal of Pathology* 1991; **164**: 307–314.
3. Watt T, Withers DJ, Martin DF, Campbell IT. *Proceedings of the Nutrition Society* 1992 (in press).

EFFECT OF LOCAL ANAESTHETIC CHOICE ON PLASMA CONCENTRATIONS OF CATECHOLAMINES DURING EXTRADURAL ANAESTHESIA

R. A. STEVENS*, D. BEARDSLEY* AND J. L. WHITE*
Departments of Anesthesiology, Uniformed Services University, Bethesda, Maryland, Medical College of Wisconsin, Milwaukee and Georgetown University, Washington, DC, USA

EXTRADURAL 0.07% BUPIVACAINE FOR POSTOPERATIVE PAIN

J. M. SLADE
Ronald Fisher Department of Anaesthetics, Poole General Hospital

It has been shown that in parturient women, analgesia obtained by infusing 0.25% bupivacaine 8 ml h^{-1} is inferior to that obtained by giving the same mass of drug as 0.07% bupivacaine 25 ml h^{-1} [1]. In this study, analgesia resulting from similar regimens is compared in patients undergoing abdominal aortic aneurysm repair.

All patients were operated on through a transverse incision and received extradural analgesia in the postoperative period. The patients were allocated randomly to one of two treatment groups. All were premedicated with lorazepam 1–2 mg and prochlorperazine 10 mg. Anaesthesia was induced with thiopentone and supplemented with doses of fentanyl up to 0.2 mg. Tracheal intubation was facilitated with vecuronium 8 mg and anaesthesia was maintained with enflurane or isoflurane in a mixture of nitrous oxide and oxygen. An extradural catheter was inserted at T9–11 and a bolus of 8 ml of 0.25% bupivacaine was given as an adjunct to anaesthesia. After surgery, the patients were transferred to the intensive care unit.

Patients in one treatment group received 0.25% extradural bupivacaine at 7 ml h^{-1}; patients in the other group received 0.07% bupivacaine 25 ml h^{-1}. All patients were given free access to i.v. boluses of alfentanil 0.05 mg given by a patient-controlled analgesia (PCA) device, the use of which had been explained to the patient on the day before surgery. The number of PCA doses received by the patient was used as a measure of the quality of the analgesia obtained from the extradural infusion.

Of the 35 patients who entered the study, 15 were withdrawn within 24 h; one patient had a fatal myocardial infarction, six were withdrawn because of protocol violations, four patients had no extradural block and four more were withdrawn when, despite demonstrable extradural blocks and frequent use of PCA alfentanil, they remained in pain. The latter four were in the 7-ml h^{-1} group. In the 20 patients who completed the study (10 in each group), the requirement for supplementary alfentanil was much lower (median three doses, range 0–16) in patients receiving bupivacaine 25 ml h^{-1} than in those receiving 7 ml h^{-1} (median 26.5 doses, range 0–50). The difference was statistically significant ($P < 0.01$, Mann–Whitney *U* test).

REFERENCE

1. Ewen A, McLeod DD, MacLeod DM, Campbell A, Tunstall ME. *Anesthesia* 1986; 41: 143–147.

EFFECT OF STOPPING SMOKING ON UPPER AIRWAY REFLEXES

R. J. ERSKINE, P. J. MURPHY AND J. A. LANGTON
University Department of Anaesthesia, Leicester Royal Infirmary

Smokers are known to present problems to anaesthetists; in particular they seem more likely than non-smokers to suffer laryngospasm and cough on induction of anaesthesia [1]. In a pilot study [2], we found that the threshold concentration of ammonia vapour required to elicit reflex glottic closure (NH_3TR) in long-term smokers was significantly lower than that of non-smokers, indicating a much greater upper airway reflex sensitivity in smokers. Furthermore, no change was found after 24 h abstinence. Therefore, the aim of this study was to determine the effect of a longer period of abstinence from smoking on upper airway reflex sensitivity.

Twenty-five subjects smoking 15 or more cigarettes daily were recruited. The baseline NH_3TR was measured in each subject using a technique described previously [3]; 13 subjects agreed to stop smoking, the remainder to carry on. Over the next 3–4 weeks, repeated measures of NH_3TR were made at regular intervals.

Eight subjects (four males), mean age 31.5 yr (range 23–51 yr), stopped smoking completely for the period of the study whilst eight others (three males), mean age 33.8 yr (range 23–48 yr), continued to smoke and acted as the control group. Nine subjects failed to complete the study.

All subjects who stopped smoking showed an increase in NH_3TR. In the majority of subjects this occurred within 7 days of stopping smoking (fig. 3).

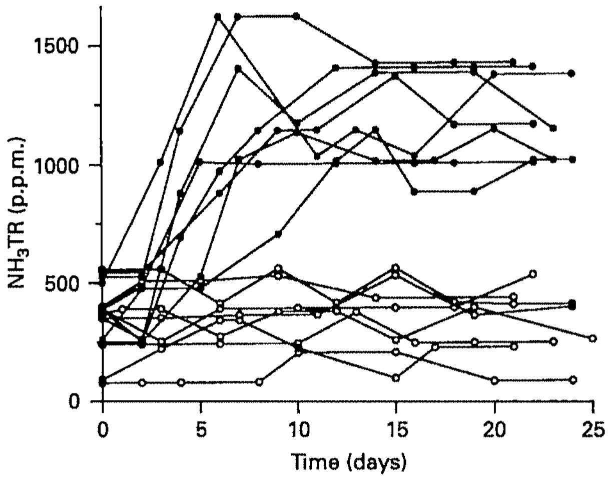


FIG. 3. Ammonia threshold concentration (NH_3TR) in smokers (○) and those who stopped smoking (●).

In conclusion, we have found that on stopping smoking there is a change in upper airway reflex sensitivity when tested using an ammonia stimulus.

REFERENCES

1. Conroy JP. *Anesthesia and Analgesia* 1969; 48: 388–400.
2. Erskine RJ, Murphy PJ, Langton JA, Smith G. *10th World Congress of Anaesthesiologists* 1992; Abstract 197.
3. Langton JA, Murphy PJ, Barker P, Smith G. *British Journal of Anaesthesia* 1991; 67: 648P.

POSTOPERATIVE LARYNGEAL FUNCTION ASSESSED BY TUSSOMETRY

J. M. LAMB*, G. E. MURTY*, R. M. SLATER AND A. R. AITKENHEAD
University Department of Anaesthesia, Queen's Medical Centre, Nottingham

Laryngeal function may be affected significantly after general anaesthesia [1]. A new non-invasive method of assessing laryngeal function by analysis of cough airflow waveform (tussometry) was used to determine if this is true.

The airflow waveform produced by a normal voluntary cough into a modified anaesthetic face mask was measured by a pneumotachograph linked to a Gaeltec flowmeter and displayed graphically as cough flow rate (litre min^{-1}) against time (ms). A normal airflow waveform shows a rapid increase to a peak—the cough peak flow rate (CPFR). The time taken to reach CPFR—the peak velocity time (PVT)—has been shown to correlate with laryngeal function in normal patients and those with vocal cord pathology [2].

Twenty unpremedicated ASA I patients undergoing peripheral orthopaedic surgery were studied. Before induction of anaesthesia, three airflow tracings were obtained in the sitting position. The shortest PVT and maximum CPFR were recorded. General anaesthesia was induced with propofol 2.2–3.8 mg kg^{-1} and fentanyl 0–1.9 µg kg^{-1} and maintained with 1–2% enflurane and 60% nitrous oxide in oxygen, administered via a laryngeal mask airway (LMA). After operation, the LMA was left *in situ* and the time (T0) of spontaneous rejection of the LMA, eye-opening, or both, was recorded.

TABLE V. *Mean difference (ms) in PVT from baseline*

Time (min)	Difference	*P* value
T10	20.90	0.0001
T20	8.95	0.0019
T30	9.27	0.02

Tussometry was performed at 10 min (T10) and 20 min (T20). Recordings were also taken at 30 min (T30) in patients with a prolonged PVT at 20 min. Differences in PVT and CPFR were compared using Student's *t* test and 95% confidence intervals for the mean differences were calculated.

Mean (SD) baseline PVT was 25.5 (4.8) ms before anaesthesia. After anaesthesia, PVT was prolonged in 19 patients at T10, in 11 patients at T20 and in five patients at T30 (table V). CPFR did not change significantly after anaesthesia. These results may reflect a temporary depression of laryngeal function associated with recovery from general anaesthesia.

REFERENCES

1. Tomlin PJ, Howarth FH, Robinson JS. *Lancet* 1968; **1**: 1402–1405.
2. Murty GE, Lancaster P, Kelly PJ. *Clinical Otolaryngology* 1991; **16**: 248–251.

ADDITION OF DROPERIDOL TO PATIENT-CONTROLLED ANALGESIA: EFFECT ON NAUSEA AND VOMITING

O. A. WILLIAMS*, F. L. CLARKE*, R. W. HARRIS*, P. SMITH* AND J. E. PEACOCK
Departments of Anaesthesia, Bassetlaw Hospital and Sheffield University Medical School

Patient-controlled analgesia (PCA) with morphine is associated with postoperative nausea and vomiting (PONV) [1]. Droperidol and morphine are stable mixed in plastic syringes for infusion [2]. The aim of this study was to assess the effect of adding droperidol to PCA morphine on PONV and antiemetic requirement.

After local Ethics Committee approval, 60 healthy female patients (aged 28–67 yr) undergoing abdominal hysterectomy were included in the study. All patients were premedicated with temazepam 20 mg and a standard anaesthetic with propofol 2 mg kg^{-1}, vecuronium 0.1 mg kg^{-1}, morphine 10 mg, droperidol 2.5 mg, 66% nitrous oxide and up to 2% isoflurane in oxygen was administered. Patients were randomized to receive either morphine 2 mg ml^{-1} (group 1) or morphine 2 mg ml^{-1} plus droperidol 0.2 mg ml^{-1} (group 2) via a Graseby PCA system with a 0.5-ml bolus and a lockout period of 5 min. All patients were prescribed rescue medication of prochlorperazine 12.5 mg 8-hourly as required. Observations were made at 4, 12 and 24 h after operation. These included four-point verbal rating scores (VRS) of nausea, vomiting, pain and sedation by one or two blinded observers. At follow-up, requirement for prochlorperazine in the 24-h study period was recorded.

Fifty-six patients completed the study, 27 in group 1 and 29 in group 2. The groups were similar in age, weight, morphine requirement and pain scores. Patients in group 2 had significantly decreased VRS for nausea at 12 h and less requirement for prochlorperazine (table VI). Sedation VRS at 24 h were significantly increased in group 2, however, no patient had to be withdrawn from the study because of sedation or other adverse effects.

TABLE VI. *Nausea, sedation and requirement for prochlorperazine in the two groups of patients.* *P < *0.05*

	Group 1	Group 2
% Patients with nausea (VRS = 0 at 12 h)	44.4	75.9*
% Patients with sedation (VRS = 0 at 24 h)	63.0	34.5*
% Patients given prochlorperazine	59.3	31.0*

Addition of low-dose droperidol to a morphine PCA reduced emetic symptoms at 12 h and decreased requirement for rescue antiemetic treatment. No adverse effects other than mild sedation were apparent.

REFERENCES

1. Macintyre PE, Runciman WB, Webb RK. *Medical Journal of Australia* 1990; **153**: 417–421.
2. Williams OA, Middleton M, Henderson P, Reilly CS. *Hospital Pharmacy Practice* 1992 (in press).

RELATIVE EFFICACY AND POTENCY OF NALMEFENE, A LONG-ACTING OPIOID ANTAGONIST

N. A. WATSON, I. T. MUNDAY AND R. M. JONES
Academic Department of Anaesthetics, St Mary's Hospital Medical School, London

Nalmefene, an analogue of naltrexone, is a potent opioid antagonist with an elimination half-life of approximately 8 h [1]. This may prevent the delayed respiratory depression often observed when naloxone (elimination half-life approximately 1 h [2]) is used to antagonize the effects of long-acting opioids. We have determined the relative potencies of nalmefene and naloxone in antagonizing fentanyl-induced respiratory depression and assessed the clinical efficacy of nalmefene.

Thirty-six patients, ASA I–III, aged 20–72 yr undergoing major elective surgery, for which moderate doses of fentanyl 4–25 µg kg^{-1} were considered appropriate, were studied. A standardized anaesthetic technique was used, including premedication with morphine 0.1 mg kg^{-1}, induction with thiopentone, neuromuscular block with vecuronium and ventilation with low concentrations of isoflurane. After antagonism of residual neuromuscular block, the following criteria were used to assess the need for postoperative opioid antagonism: ventilatory frequency less than 16 b.p.m. while intubated; ventilatory frequency less than 12 b.p.m. extubated; or a rate of 12–16 b.p.m. with arterial oxygen saturation (Sa_{O_2}) greater than 3% less than before operation. Patients were allocated randomly to receive incremental doses of nalmefene 0.25 µg kg^{-1} or naloxone 0.5 µg kg^{-1} at 5-min intervals, titrated against ventilatory frequency and Sa_{O_2}, until respiratory depression was reversed.

TABLE VII. *Mean (range) potency and clinical efficacy of nalmefene compared with naloxone.* **P < *0.01 compared with nalmefene group*

	Nalmefene (*n* = 18)	Naloxone (*n* = 18)
Duration of surgery (min)	107.9 (28–231)	129.9 (43–289)
Total dose of fentanyl (µg kg^{-1})	10.40 (5.62–25)	10.46 (4.44–22.4)
Initial dose of antagonist (1st hour) (µg kg^{-1})	0.57 (0.25–0.75)	1.11** (0.5–2.5)
Morphine dose (1st hour) (mg)	10.28 (0–20)	6.53 (0–15)
Morphine dose (1–23 h) (mg)	8.06 (0–30)	7.22 (0–30)

The potency of nalmefene was found to be approximately twice that of naloxone (table VII). After the initial dose of antagonist, three patients who received nalmefene required a total of five additional doses compared with seven naloxone patients who required a total of 37 additional doses ($0.05 < P < 0.1$, Mann–Whitney test). This suggests that the antagonism of respiratory depression by nalmefene is of greater duration than that produced by naloxone. The failure of these results to achieve statistical significance probably reflects the small sample size.

ACKNOWLEDGEMENT

This study was supported by Anaquest.

REFERENCES

1. Dixon R, Hsiao J, Taaffe W, Hahn E, Tuttle R. *Journal of Pharmaceutical Sciences* 1984; **73**: 1645–1646.
2. Ngai SH, Berkowitz BA, Yang JC, Hempstead J, Spector S. *Anesthesiology* 1976; **44**: 398–401.

ANQ 9040: EFFECT OF TWICE THE ED_{95} DOSE

I. T. MUNDAY* AND R. M. JONES
St Mary's Hospital Medical School, London

Anq 9040 is a competitive neuromuscular blocking drug with a rapid onset of action. An initial dose-finding study in 31 volunteers indicated a mild vagolytic action but no other adverse effects, and an estimated ED_{95} of 1.3 mg kg^{-1}. The aim of this study was to evaluate the effect of twice the ED_{95} dose of Anq 9040 in healthy volunteers.

Ten male volunteers were anaesthetized with a propofol infusion and ventilated with nitrous oxide in oxygen via a laryngeal mask airway. ECG, Sp_{O_2}, end-tidal carbon dioxide concentration, temperature and arterial pressure were monitored. The response of the adductor pollicis to train-of-four stimulation (12-s intervals) of the ulnar nerve was measured with a Myograph 2000. Plasma samples were obtained for histamine assay at 0, 2, 5, 10, 15 and 30 min after injection. Anq 9040 was administered over 30 s in the first seven volunteers and over 1 min in the final three volunteers. The onset time was measured from the end of injection to 100% block (i.e. 12 s after the last visible T1 response). The duration of action was measured from the end of injection until a T4/T1 ratio > 0.7.

The mean onset time for the first seven patients was 51.3 s (range 40–67 s). Mean duration of action ($n = 9$) was 45.3 min (range 35.6–60.8 min). Mean changes in heart rate, arterial pressure and plasma concentrations of histamine are shown in table VIII. At 2 min, heart rate had increased to 49 % greater than baseline and mean arterial pressure had decreased by 12%. Arterial pressure returned to baseline within 5 min but the heart rate remained increased for the duration of the experiment. Plasma concentrations of histamine were increased significantly at 2 and 5 min.

These results indicate that Anq 9040 is a rapid onset neuromuscular blocker. However, twice the ED_{95} dose is associated with significant histamine release.

TABLE VIII. *Mean (SD) changes in heart rate (HR), mean arterial pressure (MAP) and plasma concentrations of histamine after administration of Anq 9040.* *P < 0.05 (*paired* t *test*)

	Time (min)					
	0	2	5	10	15	30
Histamine	0.30	3.82*	1.05*	0.42	0.23	0.23
(ng ml^{-1})	(0.35)	(3.12)	(0.81)	(0.23)	(0.10)	(0.05)
MAP (mm Hg)	65.9	58.3*	63.2	67.1	66.3	68.1
	(6.1)	(10.4)	(10.1)	(9.0)	(8.1)	(9.8)
HR (beat min^{-1})	71.3	106.1*	101.3*	95.3*	93.9*	91.1*
	(9.5)	(16.2)	(15.3)	(13.1)	(13.5)	(11.3)

ACKNOWLEDGEMENT

This study was supported by Anaquest.

COMPARISON OF THE ONSET OF DEPOLARIZING *VS* NON-DEPOLARIZING BLOCK AFTER EARLY TOURNIQUET RELEASE IN THE ISOLATED FOREARM

J. R. HOOD*, N. CAMPKIN* AND S. A. FELDMAN
Magill Department of Anaesthetics, Westminster Hospital, London

In a previous study of the onset of vecuronium block in the isolated forearm, it was noted that if the arterial tourniquet was released at 50 % twitch depression, the block continued to increase for a further 2–3 min. This was shown not to be a result of recirculating drug [1]. Feldman and Tyrrell [2] proposed that non-depolarizing drugs were bound in the neuromuscular junction, unlike depolarizing drugs, such as decamethonium, which dissociate rapidly. This would explain the prolonged recovery after non-depolarizing agents compared with decamethonium in the isolated forearm. It is possible that such binding may maintain a concentration gradient in the biophase after early tourniquet release and explain the further increase in block seen after vecuronium. If so, decamethonium block would not exhibit this phenomenon. We have studied the onset of block produced by vecuronium, decamethonium and atracurium in the isolated forearm, after early release of the tourniquet.

Three groups of five experiments were performed on five volunteers. A vein on the dorsum of the hand was cannulated, a 2-kg strain gauge with a thumbpiece modification was secured and a standard pretension applied. The ulnar nerve at the wrist was stimulated using a supramaximal 0.2-ms square wave impulse at 0.2 Hz. The resultant adductor pollicis twitch was amplified and recorded. After stabilization, a forearm tourniquet was inflated to a pressure of 300 mm Hg. Saline 20 ml containing either vecuronium 0.3 mg (group I), atracurium 2 mg (group II) or decamethonium 0.15 mg (group III) was administered i.v. to produce paralysis by retrograde spread. These doses are equipotent in the isolated forearm. The arterial tourniquet was released at approximately 50 % twitch depression in each group. The twitch height relative to control (T1/T0) at tourniquet release and at maximal block were measured and the difference calculated; the values for each group were compared using ANOVA (table IX).

TABLE IX. *Mean (SD) twitch height relative to control (T1/T0) at tourniquet release, at maximum block and the difference between the two in patients given vecuronium (group I), atracurium (group II) and decamethonium (group III).* **P < *0.01 compared with groups I and II*

	T1/T0 (%)		
Group	At release	Max. block	Difference
I	42 (4.9)	10 (3.8)	32 (6.6)
II	48 (2.2)	16 (4.7)	32 (5.9)
III	49 (3.4)	44 (6.8)**	5 (5.8)**

Onset of depolarizing block by decamethonium in the isolated forearm is associated with minimal increase in block after early tourniquet release. Significant increases in block after early tourniquet release are seen during onset of vecuronium or atracurium block in the isolated forearm and may be a result of binding of these drugs within the biophase.

ACKNOWLEDGEMENT

This study was supported financially by Charing Cross/Westminster Hospital Trustees.

REFERENCES

1. Hood JR, Campkin N, Feldman SA. *British Journal of Anaesthesia* 1992; **69**: 535P.
2. Feldman SA, Tyrrell MF. *Proceedings of the Royal Society of Medicine* 1970; **63**: 692–695.

RECOVERY OF ATRACURIUM AND VECURONIUM NEUROMUSCULAR BLOCK IN THE ISOLATED FOREARM

J.-C. LAW MIN*, J. R. HOOD*, N. CAMPKIN* AND S. A. FELDMAN
Magill Department of Anaesthetics, Westminster Hospital, London

The duration of action of systemic injections of three times the ED_{90} of atracurium or vecuronium are similar (58.3 *vs* 52.6 min)

[1]. This occurs despite the elimination half-life of vecuronium being approximately three times greater than that of atracurium (71 min *vs* 22 min, respectively, pooled data) [2]. This discrepancy has been attributed to the differing modes of elimination of the two drugs; atracurium undergoes multicompartment elimination via Hoffmann degradation and ester hydrolysis [2]. These processes might therefore be expected to produce a more rapid recovery of atracurium block in the isolated arm experiment. The purpose of this study was to compare the blocks produced by these two drugs in bilateral isolated arm experiments, both blocks being affected by the same, small plasma concentration of drug.

Eight experiments were performed in six volunteers. A vein on the dorsum of each hand was cannulated, a 2-kg strain gauge with a thumbpiece modification was secured and a standard pretension applied. The ulnar nerve at the wrist was stimulated using a supramaximal 0.2-ms square wave impulse at 0.2 Hz. The resultant adductor pollicis twitch was amplified and recorded. After stabilization, forearm tourniquets were inflated simultaneously to pressures of 300 mm Hg. Vecuronium 0.3 mg was administered i.v. into one arm and atracurium 1.5 mg into the other. Both drugs were given in saline 20 ml to produce paralysis via retrograde spread. These doses are equipotent: 0.11 of an ED_{95} dose for a 70-kg subject. The arterial tourniquets were released together after 3 min: > 90 % twitch depression was achieved in each experiment. The 25–75 % recovery indices were measured from each hard copy and the values of the two groups compared by paired *t* test.

The mean recovery indices were significantly larger ($P < 0.01$) for atracurium (mean 11.0 (SD 1.7) min) compared with vecuronium (9.2 (0.9) min).

The results were converse to expectation. The prolonged recovery of atracurium in the isolated arm is consistent with this drug being washed more slowly out of the biophase of the arm than vecuronium, as a result of stronger affinity for binding sites within the biophase. After a systemic injection of atracurium, it is possible that this greater affinity is offset by the more rapid decrease in plasma concentrations than that of vecuronium, and the resulting greater biophase–plasma concentration gradient, so that its overall duration of action equals that of vecuronium.

ACKNOWLEDGEMENT

The study was supported financially by Charing Cross/Westminster Hospital Trustees.

REFERENCES

1. Robertson EN, Booij LH, Fragen RJ, Crul JF. *British Journal of Anaesthesia* 1983; **55**: 126–129.
2. Miller RD, Rupp SM, Fisher DM. *Anesthesiology* 1984; **61**: 444–453.

PREDICTION OF INFUSION RATE OF VECURONIUM TO MAINTAIN STEADY STATE USING THE BOLUS TEST DOSE TECHNIQUE

R. J. MORGAN AND B. J. POLLARD
Department of Anaesthesia, Manchester Royal Infirmary

A previous study [1] has demonstrated that it is possible to predict the infusion rate of vecuronium required to maintain steady state neuromuscular block by measuring the duration of action of a 4-mg bolus dose given in the presence of existing vecuronium block. That study used a Relaxograph (Datex) to measure twitch height, and provided data only for infusion rates between 2.0 and 4.0 mg h^{-1}. Therefore, we decided to re-examine this technique using a standard peripheral nerve stimulator to measure the interval between return of T1 after the loading dose and bolus dose in order to predict infusion rate.

Neuromuscular block was monitored first by a Relaxograph on the hand (the display of which was out of sight of the observer) and also by observing the movement of one great toe after stimulation of the lateral popliteal nerve. Vecuronium 0.1 mg kg^{-1} was given and on return of the first contraction of the train-of-four, a bolus of vecuronium 1, 2 or 4 mg was given. On return of the first contraction of the train-of-four again, an infusion of vecuronium was begun at a rate predicted from Harrison's study [1]. Adjustments were then made to obtain a constant level of block.

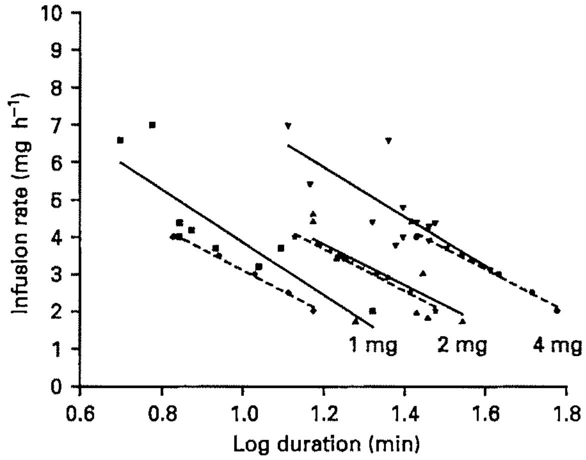


FIG. 4. Duration of action of a test dose of vecuronium when given before the infusion, compared with the infusion rate. — — — = Data from Harrison's study [1].

Results are shown in figure 4. Use of the 2-mg and 4-mg bolus test doses was not technically difficult. However, when a 1-mg bolus dose was given during the recovery phase of neuromuscular block, the difference in degree of block was imperceptible by palpation. The Relaxograph data were used for the 1-mg bolus dose.

This technique is useful for predicting the infusion rate of vecuronium during anaesthesia.

REFERENCE

1. Harrison MJ. *British Journal of Anaesthesia* 1990; **64**: 287–293.

ONSET OF ACTION OF A SMALL DOSE OF VECURONIUM

M. H. NATHANSON, C. A. McCARTNEY, C. FERGUSON AND M. J. JORDAN
Department of Anaesthesia, St Bartholomew's Hospital, London

Individual variation in the effect of a weight-based dose of a non-depolarizing neuromuscular blocking agent is well described. In 1967, Katz described the effect of a small dose of tubocurarine 0.1 mg kg^{-1} in 100 patients in which the degree of block produced varied from 0 to 100 % [1]. We studied the onset of action of vecuronium in doses equivalent to those used by Katz.

After Ethics Committee approval, informed consent was obtained from 50 healthy adult patients (26 males) aged 31–61 yr (median 45 yr) undergoing elective surgical procedures. Patients received standardized premedication and anaesthesia. Patients' lungs were ventilated to maintain end-tidal carbon dioxide concentration ($P\bar{E}'_{CO_2}$) between 4.5 and 6.2 kPa. $P\bar{E}'_{CO_2}$ and end-tidal enflurane were measured with a Datex Capnomac, and palmar skin temperature was measured with a Libra Oxygen and Temperature Monitor Model 900. A Datex Relaxograph was used to measure the electromyograph response over the hypothenar eminence of stimulation of the ulnar nerve. After calibration of the Relaxograph, the control response to a supramaximal stimulus was measured and vecuronium 0.02 mg kg^{-1} was given by bolus injection. The height of the first twitch of the train-of-four, $P\bar{E}'_{CO_2}$, end-tidal enflurane and skin temperature were measured after 5 min. The results were analysed using the StatView II (Abacus Concepts) statistical package.

The measured response of the first twitch in the train-of-four to the control response (T1/T0) ranged from 0 to 100 % (median 70 % (51–83 % interquartile range)) (fig. 5). We found no significant correlation between T1/T0 and $P\bar{E}'_{CO_2}$, end-tidal enflurane or skin temperature. There was a weak negative correlation with weight ($\rho = -0.34$, $P = 0.016$) and a weak positive correlation with age ($\rho = 0.39$, $P = 0.006$) (Spearman's rank correlation coefficient).

We have demonstrated that there is wide individual variation to

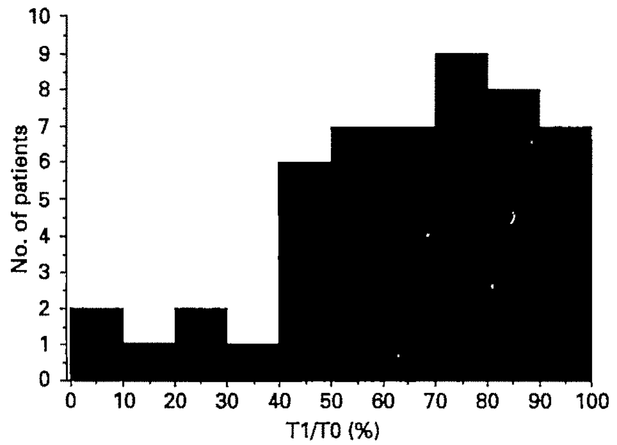


FIG. 5. Frequency distribution of T1/T0 at 5 min.

a small dose of vecuronium when the dose is calculated on a weight basis. The weak negative correlation between T1/T0 at 5 min with body weight confirms that a dose based on body weight alone tends to overestimate vecuronium requirements in heavy patients. The weak positive correlation with age may be spurious, as the block may still be developing at 5 min in the elderly patient, but more studies are necessary to confirm this. These findings may be of clinical significance when small doses of vecuronium are used for "priming".

REFERENCE

1. Katz RL. *Anesthesiology* 1967; **28**: 327–336.

USE OF PANCURONIUM AND PIPECURONIUM IN THE ICU

K. S. KHUENL-BRADY, B. REITSTÄTTER*,
A. SCHLAGER*, T. LUGER* AND S. AGOSTON*
Clinic for Anaesthesia and Intensive Care, University of Innsbruck, Innsbruck, Austria

PHARMACOKINETICS OF ROCURONIUM (ORG 9426) IN PATIENTS WITH AND WITHOUT IMPAIRED RENAL FUNCTION

R. COOPER, V. R. MADDINENI, R. K. MIRAKHUR
AND J. M. K. H. WIERDA
Departments of Anaesthesia, The Queen's University of Belfast and the University of Groningen, The Netherlands

Rocuronium (Org 9426) is a new monoquaternary aminosteroidal neuromuscular blocking agent with a duration of action similar to that of vecuronium but with a faster onset of effect [1]. Although studies in the cat have suggested the drug to be primarily excreted via the liver [2], studies by Wierda and colleagues showed that approximately 30 % of an injected dose of rocuronium is excreted by the kidneys in man [3]. In the present study we have determined the pharmacokinetics of a single bolus dose of rocuronium in patients with and without impaired renal function.

Nine patients with normal renal function and nine with chronic renal failure requiring haemodialysis were included in the study. Anaesthesia was induced with fentanyl 2–3 μg kg^{-1} and thiopentone 3–5 mg kg^{-1} and maintained with 67 % nitrous oxide in oxygen and 0.5–1 % isoflurane (inspired concentration). Neuromuscular block was measured by stimulation of the ulnar nerve with supramaximal stimuli of 0.2-ms duration, in a train-of-four (TOF) mode at 2 Hz every 1 s, and recording the force of contraction of adductor pollicis muscle. Rocuronium 0.6 mg kg^{-1} was administered after stabilization of the control responses. Venous blood samples were obtained before injection of rocuronium and at intervals for 390 min. Plasma concentrations of rocuronium were measured by high performance liquid chromatography. The data were fitted to a three-compartment model using the program Multifit. Data from one patient from each group were excluded from analysis. The results were compared using the Mann–Whitney *U* test.

TABLE X. *Mean* (SD) *pharmacokinetic variables in patients with renal failure and in control subjects.* *P < *0.05*

	Renal failure	Controls
n	8	8
Cl (ml kg^{-1} min^{-1})	2.5 (1.1)*	3.7 (1.4)
$T_{\frac{1}{2}}^{\pi}$ (min)	1.6 (0.7)	1.8 (1.5)
$T_{\frac{1}{2}}^{\alpha}$ (min)	24.3 (11.1)	14.8 (5.5)
$T_{\frac{1}{2}}^{\beta}$ (min)	104 (41.0)	97 (26.4)
V^{ss} (ml kg^{-1})	212 (47.3)	207 (48.9)
V^{c} (ml kg^{-1})	51.0 (29.2)	38.5 (21.1)
MRT (min)	97 (48.9)	58 (9.6)

The time to spontaneous recovery of T1 to 90 % of control were 101 and 69 min and to recovery of TOF ratio to 0.7, 99 and 73 min, respectively, in patients with and without renal failure ($P > 0.05$). The results of kinetic analysis are summarized in table X. Renal failure was associated with a decrease in the clearance of rocuronium, but other pharmacokinetic variables were not significantly different between the groups. This may explain the slightly longer duration of action of rocuronium observed in patients with renal failure.

REFERENCES

1. Cooper R, Mirakhur RK, Clarke RSJ, Boules Z. *British Journal of Anaesthesia* 1992; **69**: 269–273.
2. Khuenl-Brady K, Castagnoli KP, Canfell PC, Caldwell JE, Agoston S, Miller RD. *Anesthesiology* 1990; **72**: 669–674.
3. Wierda JMKH, Kleef UW, Lambalk LM, Kloppenburg WD, Agoston S. *Canadian Journal of Anaesthesia* 1991; **38**: 430–435.

LUNG FUNCTION AFTER VECURONIUM PRETREATMENT IN ELDERLY PATIENTS

R. P. MAHAJAN*, N. HENNESSY* AND
A. R. AITKENHEAD
University Department of Anaesthesia, Queen's Medical Centre, Nottingham

Pretreatment with vecuronium 0.01 mg kg^{-1} in young, healthy adults causes significant reductions in forced vital capacity (FVC), forced expiratory volume in 1 s (FEV_1), maximum mid-expiratory flow rate (MMEF), functional residual capacity (FRC) and expiratory reserve volume (ERV), although oxygen saturation ($S\mathrm{p}_{\mathrm{O}_2}$) remains unchanged [1]. This study was carried out to investigate the effect of the same pretreatment on lung function in elderly patients and to identify any clinical evidence of muscle weakness.

Informed consent was obtained from eight female patients (ASA I–II) aged 67–76 yr (mean 72.2 yr), height 1.51–1.69 m (mean 1.58 m) and weight 56–72 kg (mean 64.8 kg). Premedication comprised temazepam 10 mg, 45–60 min before surgery. The investigation was carried out in the anaesthetic room with patients in the supine position. ECG and arterial oxygen saturation were displayed continuously. Lung function (FVC, FEV_1, MMEF,

TABLE XI. *Mean* (SD) *results of lung function tests before and after administration of vecuronium.* *P < *0.05;* **P < *0.01;* ***P < *0.001*

	Before	After	% Change
FVC	2.17 (0.36)	1.97 (0.37)**	−9.6
FEV_1	1.72 (0.21)	1.61 (0.26)	−6.8
PEFR	3.15 (1.42)	3.38 (1.52)	+9.8
MMEF	2.02 (0.61)	1.89 (0.50)	−1.3
FRC	2.35 (0.62)	1.90 (0.49)**	−18.05
ERV	0.43 (0.22)	0.19 (0.12)***	−57.7
RV	1.92 (0.56)	1.71 (0.51)	−9.8
IC	2.23 (0.55)	2.19 (0.43)	−0.71
SVC	2.66 (0.56)	2.38 (0.53)*	−9.67
TLC	4.58 (0.69)	4.09 (0.63)*	−10.12
$S\mathrm{p}_{\mathrm{O}_2}$	96.60 (1.06)	93.88 (3.31)*	−2.75

peak expiratory flow rate (PEFR), FRC, ERV, residual volume (RV), inspiratory capacity (IC), slow vital capacity (SVC), total lung capacity (TLC) and Sp_{O_2}) was assessed using a Morgan transfer test machine before and 3 min after administration of vecuronium 0.01 mg kg^{-1} i.v. The results were analysed by paired Student's *t* test. All patients developed ptosis, six were unable to perform the Valsalva manoeuvre for 10 s, five had diplopia and three were unable to swallow or lift their head for > 4 s, demonstrating significant muscle weakness. Significant reductions occurred in FVC, FEV_1, FRC, ERV, SVC and TLC (table XI). Importantly, Sp_{O_2} decreased by > 4 % in four of the eight patients, causing a significant overall change.

We conclude that vecuronium pretreatment in elderly patients causes significant impairment of lung function and a significant decrease in oxygen saturation.

REFERENCE

1. Mahajan RP, Laverty J. Lung function after vecuronium pretreatment in young, healthy patients. *British Journal of Anaesthesia* 1992; **69**: 318–319.

PROPOFOL AND ALFENTANIL OR THIOPENTONE AND SUXAMETHONIUM FOR TRACHEAL INTUBATION

G. N. BECK*, G. R. MASTERSON*, J. RICHARDS* AND P. BUNTING*
Department of Anaesthesia, Royal Preston Hospital, Preston

The routine technique for rapid sequence induction usually involves the use of thiopentone and suxamethonium. The many complications of suxamethonium are well recognized and so alternative techniques are desirable. In this study, we compared the intubating conditions and haemodynamic changes during induction of anaesthesia using a standard rapid sequence induction, using propofol and alfentanil.

Sixty-four patients (ASA I and II, aged 18–60 yr) undergoing surgical procedures lasting longer than 20 min and requiring tracheal intubation were studied. After assessment of pharyngeal structures using the Mallampati test [1], the patients were preoxygenated for 3 min. Arterial pressure (Dynamap), heart rate and oxygen saturation (Ohmeda 3700E) measurements were made 3 min before induction and at 1-min intervals from induction for 4 min.

Patients were allocated randomly to two groups. In group TS, anaesthesia was induced with thiopentone 5 mg kg^{-1} over 20 s, followed by suxamethonium 1 mg kg^{-1}. Tracheal intubation was performed 40 s after administration of suxamethonium. At tracheal intubation, fentanyl 2 μg kg^{-1} was given. In group PA, anaesthesia was induced with alfentanil 50 μg kg^{-1}, followed by propofol 2 mg kg^{-1} over 30 s. Tracheal intubation was performed after a further 30 s. Thus tracheal intubation occurred 1 min after commencement of induction in both groups.

Tracheal intubation was performed by a junior anaesthetist independent of the study who recorded intubating conditions on a visual analogue scale and the grade of intubation [2]. Occurrence of coughing, laryngospasm, movement, bronchospasm or other significant complication was recorded.

The groups were comparable in age, sex and weight. There was no significant difference between the Mallampati, Cormack and Lehane and visual analogue scores between the two groups (chi-square and Mann–Whitney tests). However, two patients in group TS did require a second dose of suxamethonium, and a third sustained initial oesophageal intubation. No such additional intervention was required in group PA. Group PA showed a significant decrease in arterial pressure and heart rate after induction, whereas group TS showed a significant increase in arterial pressure and heart rate (table XII).

We conclude that rapid tracheal intubation can be performed reliably using the regimen described, avoiding the use of suxamethonium. This technique may be of use in patients where a decrease in arterial pressure and heart rate is preferable to an increase in arterial pressure and heart rate during a rapid sequence induction and warrants further investigation.

REFERENCES

1. Mallampati SR, Gatt SP, Gugino LD. *Canadian Anaesthetists Society Journal* 1985; **32**: 429–434.
2. Cormack RS, Lehane J. *Anaesthesia* 1984; **39**: 1105–1111.

VALIDATION OF COHERENT FREQUENCY OF THE EEG AS A MEASURE OF CONSCIOUSNESS DURING ANAESTHESIA

R. MUNGLANI*, J. ANDRADE*, D. J. SAPSFORD, A. BADDELEY* AND J. G. JONES
Cambridge University Department of Anaesthesia and MRC Applied Psychology Unit, Cambridge

The amplitude of the 40-Hz auditory steady state response (SSR) has been proposed as an indicator of consciousness during anaesthesia [1]. However, we showed that this signal disappears in awake subjects with very light anaesthesia [2]. We examined the relationship between the change in SSR and in cognition during the inhalation of a range of isoflurane concentrations.

The SSR was examined in response to a range of auditory clicks from 47 to 5 Hz, presented sequentially in seven subjects who inhaled end-tidal isoflurane concentrations increasing stepwise from 0–0.8 %. At two points in the study, a painful stimulus was given. During the study, category recognition (CR) and within list recognition (WLR) were used to test psychological function. After the study, implicit and explicit memory were tested for stimuli and events during the study period. At each stimulating frequency, 100 samples of EEG were recorded, averaged and a Fourier transform applied to obtain a frequency–power spectrum. Three components were seen: the fundamental (P*f*), and the first and second harmonics (P_1 and P_2). Analysis showed that at certain coherent frequencies (CF), the power in the fundamental was large with little power in the harmonics. Frequencies either side of the CF did not show this pattern. To extract these CF, a manipulation was applied so that if $(P_1+P_2) >$ 30 % P*f* then a value of 0 was given to P*f*, otherwise P*f* was left at its original value. Data were then transformed so that the resultant power, $P_r = (Pf/(P_1+P_2)) \times Pf$. If more than one CF appeared, a weighted average coherent frequency (aCF) was used.

There was a decrease in aCF, CR and WLR with increasing concentration of isoflurane. Painful stimulation caused an increase in all variables (ns). The aCF correlated best with WLR (r = 0.343, Spearman, P = 0.028). On recovery, a category generation task showed no evidence of learning at 0.8 % isoflurane. The aCF

TABLE XII. *Changes in heart rate (HR), systolic (SAP) and diastolic (DAP) arterial pressure (mean (SD)) before and after tracheal intubation in the two groups of patients.* ** $P < 0.01$ *compared with mean preincubation values*

	SAP		DAP		HR	
	Group TS	Group PA	Group TS	Group PA	Group TS	Group PA
Mean preinduction	134	128	80	74	84	84
	(21)	(17)	(12)	(11)	(16)	(17)
Mean postinduction	142**	105**	91**	59**	98**	73**
	(16)	(21)	(11)	(14)	(18)	(15)
Maximum postinduction	165**	117	108**	69	111**	80
	(24)	(23)	(16)	(16)	(21)	(18)
Minimum postinduction	122	94**	74	51**	86	66**
	(16)	(20)	(13)	(14)	(20)	(14)

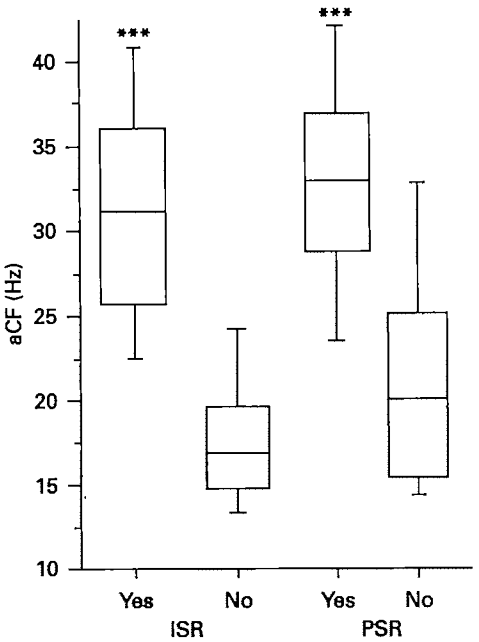


FIG. 6. Average coherent frequency (aCF) associated with intra-study response (ISR) or post-study explicit recall of intra-study events (PSR): 61 data points from seven subjects for each variable. The edge of the box plots represents the 25th or 75th centiles, the error bars represent the 10th or 90th centiles. ***$P = 0.001$, Mann–Whitney U test.

values at each isoflurane concentration were correlated with the presence or absence of any responses to command and post-study explicit memory for intra-study events. These data are presented in figure 6 and show a highly significant difference between the aCF values seen with and without responsiveness or with or without explicit memory.

REFERENCES

1. Plourde G, Picton T. *Anesthesia and Analgesia* 1990; 71: 460–468.
2. Sapsford DJ, Munglani R, Jones JG, Fitzgerald WJ. *Anaesthesia* 1992 (in press).

DOES PROPOFOL SUPPLEMENTED ANAESTHESIA AFFECT NEUROPHYSIOLOGICAL OUTCOME FOLLOWING CARDIOPULMONARY BYPASS?

A. S. PHILLIPS*, C. M. McDAID, T. J. McMURRAY AND S. A. LEWIS

Departments of Anaesthetics and Mental Health, The Queen's University of Belfast and the Royal Victoria Hospital, Belfast

Deficit in cognitive functioning has been reported after cardiopulmonary bypass (CPB) which may be greater after valve replacement than after coronary artery bypass grafting (CABG) [1]. It has been suggested that propofol may have cerebral protective properties [2] which could affect neuropsychological outcome. The present study compares the neuropsychological outcome after propofol or isoflurane supplemented fentanyl anaesthesia in patients undergoing valve replacement or CABG.

Forty-one patients undergoing CABG and 20 undergoing valve replacement were included in the study. Patients with neurological dysfunction, evidence of carotid artery disease or long-term benzodiazepine therapy were excluded. Premedication comprised morphine 0.1–0.15 mg kg^{-1}, hyoscine 0.2–0.3 mg and lorazepam 2–3 mg. After induction of anaesthesia with fentanyl 25 μg kg^{-1} patients were allocated randomly to supplementation with propofol 1–10 mg kg^{-1} h^{-1} or 0–2.0 % isoflurane which was continued during CPB. Patients' lungs were ventilated with oxygen-enriched air and additional fentanyl given at sternotomy, start of CPB and rewarming. A constant flow rate was maintained during CPB using a bubble oxygenator and perfusion pressure was maintained

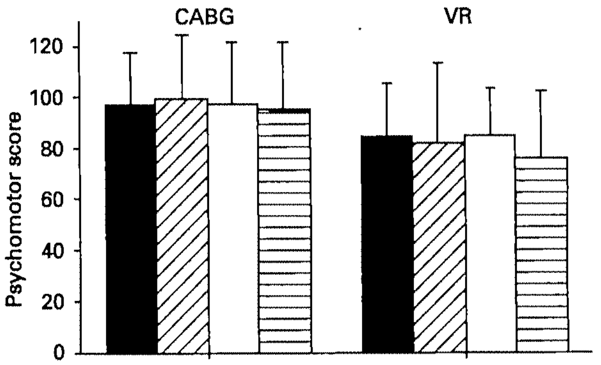


FIG. 7. Mean (SD) psychomotor speed scores in patients undergoing coronary artery bypass grafting (CABG) or valve replacement (VR) before operation in the propofol (■) and isoflurane (□) groups and on day 7 after operation in the propofol (▨) and isoflurane groups (▤).

between 40 and 60 mm Hg and P_{O_2} between 13.3 and 26.7 kPa, using alpha stat criteria. Patients were assessed with a battery of standard psychometric tests before operation and on day 2 and day 7 after operation. These tests measured memory, visiospatial skills, mood and psychomotor speed. Results were compared using analysis of variance.

Analysis of preoperative performance showed that patients undergoing valve replacement had significantly smaller scores in some tests. Performance in all groups was impaired on day 2. However, it had returned to preoperative values by day 7 in most patients as represented by changes in psychomotor speed (fig. 7). The change in performance from baseline to day 2 and day 7 was similar in both CABG and valve replacement patients. There was no significant difference within each surgical group between patients receiving propofol or isoflurane.

REFERENCES

1. Slogoff S, Girgis KZ, Keats AS. *Anesthesia and Analgesia* 1982; 61: 903–911.
2. Stephan H, Sonntag H, Schenk HD, Kohlhausen S. *Anesthesist* 1987; 36: 60–65.

HALOTHANE, METABOLITE-INDUCED ANTIBODIES AND HEPATOTOXICITY

J. G. KENNA* AND T. L. KNIGHT*

Department of Pharmacology and Toxicology, St Mary's Hospital Medical School, London

A variety of clinical and laboratory findings suggest strongly that immune reactions play a pathogenic role in the severe form of halothane-induced liver damage, commonly termed "halothane hepatitis" [1, 2]. In particular, previous studies have established that sera from a high proportion of patients with halothane hepatitis contain antibodies to halothane metabolite-modified liver protein antigens, and have implicated this antibody response in the mechanism of liver damage [2]. The metabolite-modified protein antigens comprise a group of at least seven distinct trifluoroacetylated liver microsomal proteins, most of which have been purified and characterized biochemically [2]. Antibodies to the trifluoroacetyl protein antigens have not been detected in a wide variety of control sera, including sera from halothane-exposed patients without evidence of liver damage [2]. It appears that all halothane-exposed individuals produce the antigens, but only a small fraction of susceptible patients mount an immune response and develop hepatitis [2].

Because the antibody response to trifluoroacetyl protein antigens is highly specific for patients with halothane hepatitis, detection of the antibodies is of diagnostic value and we are frequently contacted by physicians who wish us to perform antibody testing. The method we use is an immunoblotting technique, in which liver microsomal fractions from halothane-treated rats are used as the source of test antigen [2]. In the last 2 yr we have been sent serum samples from 12 patients who developed otherwise unexplained liver damage after a recent halothane anaesthetic. We report the results we have obtained.

We received six sera in 1991 from adult British patients. Two patients developed liver failure and underwent liver transplantation; one died. Antibodies to trifluoroacetyl protein antigens were detected in two sera (33 %). In 1992, we received sera from a further six adult patients, four from the U.K., one from Spain and one from the Netherlands. Two of these patients developed encephalopathy and one underwent successful liver transplantation. Antibodies to trifluoroacetyl protein antigens were detected in four of the sera (67 %). Clearly halothane hepatitis continues to be a clinical problem in the U.K. and in Europe.

ACKNOWLEDGEMENT

The authors thank the Wellcome Trust for financial support.

REFERENCES

1. Ray DC, Drummond GB. *British Journal of Anaesthesia* 1991; **67**: 84–99.
2. Kenna JG. *Biochemical Society Transactions* 1991; **19**: 191–195.

EFFECT OF FENTANYL ON [^{3}H]NORADRENALINE UPTAKE IN ISOLATED NEURONAL CELL PREPARATIONS

R. ATCHESON, D. J. ROWBOTHAM AND D. G. LAMBERT
University Department of Anaesthesia, Leicester Royal Infirmary

The cellular mechanisms by which opioids produce their clinical effect may include a decrease in neurotransmitter release. In a previous study, we have demonstrated that fentanyl inhibits the evoked release of [^{3}H]noradrenaline from a neuronal cell preparation [1]. Evidence suggests that opioids may also modulate transmitter uptake. Indeed, tramadol, a weak opioid receptor agonist, inhibits uptake of noradrenaline and this may contribute to its analgesic effect [2]. We have utilized two cell lines, a differentiated human neuroblastoma (SH-SY5Y) and a rat phaeochromocytoma (PC12), to examine opioid modulation of noradrenaline uptake.

Cells cultured as a monolayer were incubated with [^{3}H]noradrenaline 40 nmol litre^{-1} in Krebs–HEPES buffer for 1 h, in the absence or presence of fentanyl 0.1–10 μmol litre^{-1}. Excess [^{3}H]noradrenaline was washed from the monolayer and [^{3}H]noradrenaline taken up by the cells was extracted with perchloric acid 0.4 mol litre^{-1}. Data were analysed using Student's paired t test.

TABLE XIII. *Mean* (SEM) *inhibition of* [^{3}H]*noradrenaline uptake by fentanyl in the two cell lines as percentage of the total uptake of* [^{3}H]*noradrenaline in the absence of fentanyl* ($n = 5$–30)

Fentanyl (μmol litre^{-1})	Inhibition (%)	
	PC12	SH-SY5Y
0.1	10.9 (3.0)	3.5 (2.0)
0.3	20.7 (3.2)	17.3 (3.4)
1.0	37.8 (1.7)	26.2 (1.6)
10.0	73.9 (0.9)	58.2 (1.6)

[^{3}H]Noradrenaline uptake was reduced significantly by fentanyl from 0.1 μmol litre^{-1} in PC12 cells ($P < 0.05$) and from 0.3 μmol litre^{-1} in SH-SY5Y cells ($P < 0.05$) (table XIII). Although these concentrations of fentanyl are within the clinical range, it is unclear if this effect plays a significant role in the production of clinical analgesia.

ACKNOWLEDGEMENT

R. Atcheson is a *British Journal of Anaesthesia* research fellow.

REFERENCES

1. Atcheson R, Lambert DG, Rowbotham DJ. *British Journal of Anaesthesia* 1992; **69**: 531P.
2. Raffa RB, Friderichs E, Reimann W, Shank RP, Codd EE, Vaught JL. *Journal of Pharmacology and Experimental Therapeutics* 1992; **260**: 275–285.

POSTER PRESENTATIONS

EVALUATION OF THE RASCAL II MONITOR

E. PALAYIWA*, E. GRINT*, J. WINYARD*, P. J. FLYNN AND L. STRUNIN
Nuffield Department of Anaesthetics, John Radcliffe Hospital, Oxford and Anaesthetics Units, The London Hospital Medical College, London

The Ohmeda Rascal II monitor utilizes Raman scattering spectroscopy [1] to provide continuous real-time and trend measurement of anaesthetic and respiratory gases. In the monitor, a helium–neon laser interacts with a flowing gas sample that is continuously drawn from the patient breathing circuit. The molecules of each respiratory and anaesthetic gas in the sample give off distinct Raman scattered light with characteristic wavelengths when irradiated by the laser beam. The number of scattered photons for each wavelength is directly proportional to the concentration of a particular gas present. The sensor uses proprietary filters and photon-counting circuits to digitally measure the scattered photon flux at multiple wavelengths. Avalanche photodiodes are used to detect the gas signals which are processed and converted to volume percent gas concentrations. The machine identifies, quantifies and displays inspired and expired concentrations of oxygen, nitrous oxide, nitrogen, carbon dioxide, halothane, enflurane and isoflurane. The monitor can distinguish mixtures of volatile agents. In this latter case the agents are identified and displayed separately.

The accuracy and response times of the Raman spectrometer were evaluated in a laboratory study and the results obtained (table XIV) compared with similar studies of the Datex Capnomac [2] and the Brüel and Kjær monitor 1304 [3]. The responses of the Rascal II were found to be within the manufacturer's specifications for oxygen, nitrous oxide, nitrogen, carbon dioxide and halothane. It was less accurate for large concentrations of enflurane and isoflurane. It was unaffected by water vapour. In the clinical setting the machine was used during semi-open and closed circuit anaesthesia. All clinicians commented on its ease of operation and clear displays.

The Rascal II monitor is a multigas analyser which includes measurement of nitrogen and specific identification of anaesthetic vapours. Comparison with the Datex Capnomac and the Brüel and Kjær monitor was favourable in the clinical range.

REFERENCES

1. Raman CV, Krishnan KS. *Nature* 1928; **121**: 501–502.
2. McPeak H, Palayiwa E, Madgwick R, Sykes MK. *Anaesthesia* 1988; **43**: 1035–1041.
3. McPeak HB, Palayiwa E, Robinson GC, Sykes MK. *Anaesthesia* 1992; **47**: 41–47.

TABLE XIV. *Accuracy and response times of the Rascal II (Rasc.), Datex Capnomac (Capn.) and Brüel and Kjær monitor 1304 (B+K) in the presence of oxygen (O_2), nitrous oxide (N_2O), nitrogen (N_2), carbon dioxide (CO_2), halothane (Hal.), enflurane (Enf.) and isoflurane (Iso.). NA = Not available.*

	Accuracy (± % v/v)			Response times (ms)		
Gas	Rasc.	Capn.	B+K	Rasc.	Capn.	B+K
O_2	1	2	1	200	290	< 360
N_2O	1	2	1	300	370	< 270
N_2	1	NA	NA	200	NA	NA
CO_2	0.2	0.5	0.2	440	210	< 360
Hal.	0.25	0.2	0.1	450	730	< 360
Enf.	0.4	0.4	0.2			
Iso.	0.6	0.2	0.25			

HALOTHANE ENHANCES FORSKOLIN STIMULATED CYCLIC ADENOSINE-3′,5′-MONOPHOSPHATE FORMATION IN HUMAN NEUROBLASTOMA CELLS

R. A. HIRST AND D. G. LAMBERT
Department of Anaesthesia, University of Leicester, Leicester Royal Infirmary

As part of a broader programme of research examining the effects of anaesthetic agents on neuronal signal transduction, we have examined the effects of the volatile anaesthetic agent halothane on cyclic adenosine-3′,5′-monophosphate (cAMP) generation in a simple homogenous neuronal cell line of human origin (SH-SY5Y).

cAMP was measured in suspensions of intact cells. The incubation cocktail (300 μl) contained the phosphodiesterase inhibitor, 3-isobutyl-1-methyl xanthine 1 mmol $litre^{-1}$, in the presence or absence of forskolin 10 μmol $litre^{-1}$ to directly activate adenylate cyclase. Reactions were terminated and cAMP extracted as described previously [1]. Halothane was delivered to the reaction using a calibrated Fluotec 3 vaporizer set at 1 % with humidified air as the carrier gas. For control incubations, air alone was used. Data were analysed using the unpaired Student's *t* test.

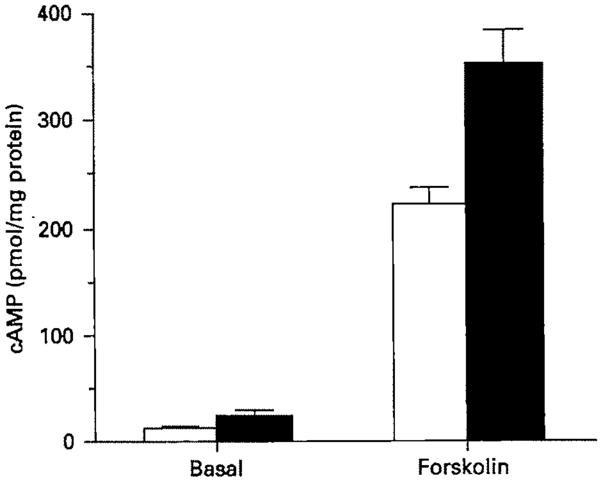


FIG. 8. Effect of halothane (■) on basal (30 min, no forskolin) and forskolin-stimulated (15 min preincubation + 15 min forskolin) cAMP formation. For control incubations, air (□) alone was used.

Halothane at a concentration of 1 % caused significant ($P <$ 0.005) potentiation (60 %) of forskolin-stimulated cAMP formation (fig. 8). The mechanisms underlying this potentiation are currently under investigation and could relate to changes in membrane fluidity at the lipid protein interface or perhaps the effect is secondary to increased intracellular calcium.

REFERENCE

1. Brown BL, Albano JDM, Ekins RP, Sgherzi AM. *Biochemical Journal* 1971; 121: 516–552.

PREOXYGENATION AND Sp_{O_2} AFTER INDUCTION OF ANAESTHESIA WITH PROPOFOL AND FENTANYL

D. B. RITTOO*, N. BREED* AND B. J. POLLARD
Departments of Anaesthesia, Hope Hospital, Salford, Royal Lancaster Infirmary, Lancaster and University Department of Anaesthesia, Manchester Royal Infirmary

The introduction of pulse oximeters has increased awareness of arterial desaturation after induction of anaesthesia. We studied prospectively the course of pulse oximeter oxygen saturation (Sp_{O_2}) after induction of anaesthesia with fentanyl and propofol in 29 ASA I patients in whom a laryngeal mask airway (LMA) was inserted.

Patients were allocated randomly into three groups. None of the patients was obese or had any contraindications to the use of propofol, fentanyl or LMA, and there was no history of smoking, chronic respiratory disease, recent chest infection or nasal obstruction. On arrival in the anaesthetic room, arterial pressures were measured and ECG and pulse oximetry monitoring was established. The Ohmeda BIOX 3700e pulse oximeter, set in the fast response mode (3-s update) with finger probe, was used. All patients were unpremedicated and received fentanyl 100 μg i.v. through a 20-gauge cannula in the dorsum of the hand followed by a sleep dose of propofol (3 mg kg^{-1}) over 10–20 s. The LMA (size 3 for females and 4 for males) was inserted at the earliest opportunity. The LMA was connected to a Bain circuit delivering 66 % nitrous oxide in oxygen and 1 % isoflurane. Two gentle positive pressure breaths were administered to verify LMA placement. Ventilation was supported with the preset gas mixture if Sp_{O_2} decreased to less than 90 %.

Group A ($n = 9$; age 21–47 yr; weight 50–80 kg) received no preoxygenation; group B ($n = 10$; age 17–46 yr; weight 50–80 kg) received oxygen 7 litre min^{-1} through a Uno-Plast, 10-French gauge nasal cannula with foam collar in one nostril for 3 min before induction of anaesthesia. These patients were free to talk and nose or mouth breathe during this period; group C ($n = 10$; age 19–37 yr; weight 52–75 kg) breathed oxygen at 8 litre min^{-1} from a face mask on a Bain circuit first flushed with oxygen. The face mask was applied by the operating department assistant at the start of injection of propofol and the patient asked to breathe normally while falling asleep. Sp_{O_2} was recorded every 10 s for up to 230 s. "Tolerated apnoea time", defined as time to return of spontaneous visible ventilatory reservoir bag movements or to application of controlled ventilation, was recorded.

Mean tolerated apnoea time in groups A, B and C were 55, 215 and 200 s, respectively. All patients in group A (no preoxygenation) had Sp_{O_2} values less than 90 %, 60 s after induction. All patients in group B (nasal cannula) maintained large Sp_{O_2} values during the period 0–230 s (range 96–100 %). Two patients in group C (face mask) had Sp_{O_2} values less than 90 % at 120 and 140 s, respectively. In both cases the initial dose of propofol was found to be inadequate and LMA insertion was prolonged. The Sp_{O_2} values of the remaining patients were 95–100 % for the period 0–230 s.

Preoxygenation by nasal cannula for 3 min or by face mask during induction eliminates the incidence of early desaturation associated with propofol and fentanyl induction.

CARDIOVASCULAR EFFECTS OF A PANCURONIUM–VECURONIUM MIXTURE

M. DOYLE*, D. MANNION*, D. McCOY*,
M. O'REGAN*, C. COONEY AND G. FITZPATRICK
Department of Anaesthesia and Critical Care, Meath Hospital, Dublin

Although vecuronium appears to be free of intrinsic cardiovascular effects [1], there have been reports of bradycardia during its use. Pancuronium can be associated with increases in heart rate (HR) and mean arterial pressure (MAP) [2]. We investigated the cardiovascular effects of a pancuronium–vecuronium mixture.

Ethics Committee approval and informed consent were obtained from 73 patients undergoing varicose vein surgery. Patients were allocated randomly to receive either pancuronium (group A, $n = 25$), vecuronium (group B, $n = 23$), or a combination of pancuronium and vecuronium (group C, $n = 25$). The neuromuscular blockers were prepared in a 5-ml syringe as follows: group A, pancuronium 8 mg in 4 ml; group B, vecuronium 8 mg in 4 ml; group C, pancuronium 4 mg plus vecuronium 4 mg in 4 ml. The anaesthetist was unaware of which drug was being used. After premedication with diazepam, anaesthesia was induced with fentanyl 2 μg kg^{-1}, droperidol 0.5 mg, thiopentone 3–5 mg kg^{-1} and 0.05 ml kg^{-1} of neuromuscular blocker. Anaesthesia was maintained with nitrous oxide in oxygen and enflurane. The trachea was intubated and the lungs ventilated mechanically. A 1-ml top-up of neuromuscular blocker was administered on recovery of two responses to a train-of-four stimulation. HR and MAP were recorded before induction, at 1-min intervals for 4 min after induction, at 1-min intervals for 5 min after intubation, before top-up and at 1-min intervals for 3 min after top-up. Significant changes in HR and MAP (±20 %) during anaesthesia were recorded.

There were no significant differences in HR or MAP between patients receiving pancuronium alone and those receiving the

TABLE XV. *Incidence of significant changes in heart rate (HR) in the three groups.* ** P < 0.01

Group	⩾ 20 % Increase in HR at intubation		⩾ 20 % Decrease in HR at any stage		HR < 50 beat min⁻¹	
	No.	%	No.	%	No.	%
Pancuronium ($n = 25$)	17	68	1	4	0	
Vecuronium ($n = 23$)	8**	32	21**	91	8**	35
Pancuronium + vecuronium ($n = 25$)	21	84	3	12	0	

combination mixture. The vecuronium group had a lower HR after induction and intubation than the other two groups ($P < 0.01$, ANOVA). After induction, MAP in the vecuronium group was less than that in the combination group ($P < 0.05$). The frequency of bradycardia (HR < 50 beat min^{-1}) was greater in patients receiving vecuronium alone ($P < 0.01$, Fisher exact test) (table XV). Bradycardia was precipitated by skin incision in two patients and by vein stripping in five patients.

This study suggests that a combination of pancuronium and vecuronium has no clinical advantage in terms of cardiovascular effects compared with pancuronium alone. While vecuronium was associated with a lower HR after induction and intubation it was also associated with a higher incidence of bradycardia.

REFERENCES

1. Booij L, Edwards R, Sohn Y, Miller RD. *Anesthesia and Analgesia* 1980; 59: 26–30.
2. Kelman GR, Kennedy BR. *British Journal of Anaesthesia* 1971; 43: 335–338.

PHARMACOKINETICS OF THE ISOMERS OF MIVACURIUM CHLORIDE IN THE HEALTHY ADULT

A. G. HEAD-RAPSON, J. C. DEVLIN, G. G. LOVELL*, C. J. R. PARKER AND J. M. HUNTER

University Department of Anaesthesia, Royal Liverpool Hospital and Wellcome Research Laboratories, Beckenham

A solution of mivacurium chloride contains three non-interchangeable stereoisomers: *trans-trans* (57 %), *cis-trans* (37 %) and *cis-cis* (6 %). The aim of this study was to determine the pharmacokinetic parameters of each isomer in healthy subjects.

Five patients weighing between 67 and 85 kg and undergoing intermediate surgery were studied. As mivacurium is known to be metabolized by plasma cholinesterase, the activity of this enzyme was measured before operation [1]. After premedication with oral diazepam 10 mg, anaesthesia was induced with fentanyl 1 μg kg^{-1} and thiopentone 3–5 mg kg^{-1} and maintained with 0.5 % isoflurane (end-tidal) and 70 % nitrous oxide in oxygen. An i.v. cannula for infusion of mivacurium chloride was inserted in one forearm and a 14-gauge cannula placed in the contralateral arm for blood sampling. After a baseline blood sample had been obtained, mivacurium chloride 15 μg kg^{-1} min^{-1} was infused over 10 min using an Ohmeda 9000 infusion pump. The pharmacodynamic response to the neuromuscular blocking agent was measured electromyographically throughout anaesthesia. Blood samples (7 ml) were obtained at 1, 2, 4, 6, 8, 10, 11, 12, 14, 16, 19, 22, 25, 30, 40, 70, 100, 130 and 190 min after starting the infusion of mivacurium and placed immediately into lithium–heparin bottles containing phospholine iodide 5 mg to inhibit plasma cholinesterase. After separation, the plasma samples were frozen until analysis. Mivacurium was extracted from the plasma using a solid-phase technique. The isomers were separated using high performance liquid chromatography and assayed fluorometrically. Mean residence time (MRT), clearance (*Cl*) and volume of distribution (V^{ss}) were calculated for each isomer using non-compartmental analysis [2].

Three males and two females aged between 31 and 58 yr were studied. The range of cholinesterase activity was 890–1280 u litre^{-1} (normal range 620–1370 u litre^{-1}). Mean (range) pharmacokinetic parameters are shown in table XVI. Clearance of the *cis-trans* and *trans-trans*, but not the *cis-cis* isomer, was found to correlate significantly with plasma cholinesterase activity ($r = 0.991$, $P < 0.01$, for both isomers).

TABLE XVI. *Mean (range) pharmacokinetic variables for the three mivacurium isomers*

	Mivacurium isomer		
	trans-trans	*cis-trans*	*cis-cis*
MRT (min)	2.9 (1.7–4.0)	2.1 (0.8–2.8)	42.3 (31.4–56.3)
Cl (ml kg^{-1} min^{-1})	70 (31–94)	138 (52–204)	5.7 (3.7–7.1)
V^{ss} (ml kg^{-1})	185 (123–268)	273 (129–452)	236 (182–341)

The *cis-trans* isomer has the greatest clearance, being twice as rapid as the *trans-trans* isomer. The *cis-cis* isomer has a much lower clearance and longer MRT than the other two isomers. The clearance of the two short acting isomers appears to correlate with plasma cholinesterase activity.

ACKNOWLEDGEMENT

This study was supported in part by a grant from Wellcome Foundation plc.

REFERENCES

1. Kalow W, Genest K. *Canadian Journal of Biochemistry* 1957; 35: 339.
2. Gibaldi M, Perrier D. *Pharmacokinetics*, 2nd Ed. New York: Marcel Dekker, 1982.

ASYMMETRY OF UPTAKE AND WASHOUT OF INERT GASES—LESSONS LEARNT IN AN ANAESTHETIC DEPARTMENT

V. FLOOK

Department of Biomedical Sciences, University of Aberdeen

It has always been assumed that the observed asymmetry between uptake and washout of inert gas during decompression is a result of bubble formation [1]. The partition coefficients of inert gases used in diving are very much less than 1.0 in all body tissues. This means that once formed, the gas phase represents a large sink for the dissolved gas and could decrease significantly the partial pressure of inert gas in the surrounding tissue, thereby reducing the driving pressure for gas to move into the blood. In addition, large numbers of vascular bubbles in capillaries may reduce or prevent blood flow, thereby slowing the removal of gas from affected areas.

In fact the asymmetry can be a consequence of the exponential nature of gas dynamics. Figure 9 shows that in fast tissues (i.e. those with short time constants) which reach saturation before the decompression starts, uptake and washout are indeed symmetrical. Compartments with long time constants compared with the time at depth, begin the decompression before reaching saturation, and in these compartments washout is considerably prolonged (fig. 9).

This is a result of the greatly reduced partial pressure gradient between tissue and incoming blood in these slow tissues. Previously published work which has used asymmetry as an

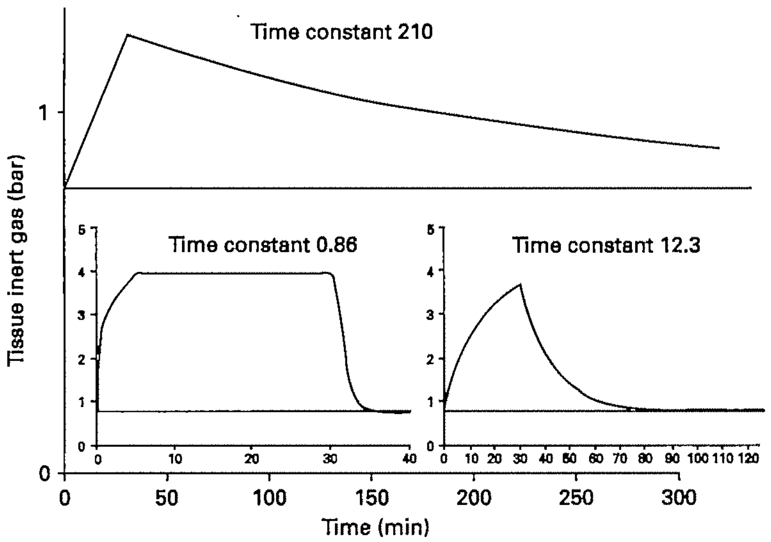


FIG. 9. Gas uptake and elimination for a slow compartment (time constant 210) and for two fast compartments (inserts) for a 2-min decompression after 30 min at 40 m.

indirect indication of the presence of bubbles must be reassessed and the early results from such a reassessment will be presented.

REFERENCE

1. Hempleman HV. *The Physiology and Medicine of Diving*. London: Baillière Tindall, 1992.

ROUTINE PREOXYGENATION: HOW LONG BEFORE MASK ANAESTHESIA?

A. G. HEAD-RAPSON AND S. L. SNOWDON
University Department of Anaesthesia, Royal Liverpool University Hospital

Arterial desaturation has been shown to be a common event during routine induction of mask anaesthesia, but in the U.K., preoxygenation is not always performed routinely, one reason given for this is lack of time. A more rapid means of preoxygenation, by three large breaths, has been advocated [1] but doubts have been cast on its efficacy [2]. Therefore, we decided to assess the efficacy of preoxygenation performed for only brief durations.

Four methods of preoxygenation were assessed using a Mapleson A breathing system: formal 2 min preoxygenation (oxygen 8 litre min^{-1}), three large breaths (oxygen 8 litre min^{-1}), three large breaths (oxygen 34 litre min^{-1}), one large breath (oxygen 34 litre min^{-1}). In a preliminary study of three healthy volunteers, the end-tidal oxygen achieved by the four different methods of preoxygenation was measured on a breath-by-breath basis using a mass spectrometer (Medishield MS2). Further studies of the effectiveness of each method were performed using a rebreathing system, with continuous monitoring of end-tidal oxygen using the mass spectrometer and of oxygen saturation using a pulse oximeter (Novametrix 500); the rate of desaturation could then be timed.

In one volunteer, the rebreathing bag consistently became empty before desaturation had occurred, except when not preoxygenated and this led us to consider the mechanisms of desaturation at the end of preoxygenation (table XVII).

TABLE XVII. *End-tidal oxygen concentration* (E'_{O_2}) *and time to* Sp_{O_2} *value of 90% during four methods of preoxygenation*

	E'_{O_2} achieved (%)	Time to Sp_{O_2} 90% (min)	E'_{O_2} final (%)
No preoxygenation	15	1.75	7
2 min (8 litre min^{-1})	80	9	7
3 breaths (8 litre min^{-1})	33	Bag empty at 5.25 min	8.5
3 breaths (34 litre min^{-1})	59	Bag empty at 6.9 min	38
1 breath (34 litre min^{-1})	44	Bag empty at 9.5 min	7

In the patient with an obstructed airway, uptake of oxygen volume is not balanced by a return of an equal volume of carbon dioxide, since 90% of carbon dioxide is stored in the body. Oxygen uptake is then associated with a decrease in lung volume until residual volume is reached. At this point, further reduction in volume may increase the shunt and cause gross changes in Sp_{O_2}. As long as the percentage of oxygen is greater than 7% (the level at which $Sp_{O_2} = 90\%$) at this limiting volume, adequate preoxygenation will have been achieved. With this assumption, the end-tidal oxygen concentration that needs to be reached to give adequate preoxygenation can be calculated given oxygen uptake and the residual volume. Three large breaths of oxygen (34 litre min^{-1}) would seem likely to achieve this level of end-tidal oxygen concentration for a large range of values of $\dot{V}O_2$ and residual volume.

REFERENCES

1. Drummond GB, Park GR. *British Journal of Anaesthesia* 1984; 56: 987.
2. Valentine SJ, Marjot R, Monk CR. *Anesthesia and Analgesia* 1990; 71: 516.

British Journal of Anaesthesia 1993; **70**: 489–494

CORRESPONDENCE

LUMBOVERTEBRAL SYNDROME AFTER EXTRADURAL BLOOD PATCH

Sir,—I read with interest the case report of Seeberger and Urwyler [1] describing severe back pain after extradural blood patch (EBP). I recently managed a patient with an almost identical problem, and I dispute the authors' conclusions that "this complication ... does not place into question the value of therapeutic EBP".

Whilst relief of headache after EBP is indeed dramatic for many patients, the findings of a large survey of inadvertent dural punctures occurring over a 20-yr period at Birmingham Maternity Hospital [2] are not as encouraging as earlier reports—EBP successfully relieved headache in only 69% of 135 patients (including seven cases requiring repeat blood patch). The same survey revealed that it is unusual for post-dural puncture headache to last for more than 10 days. In common with the patient described in the case report, my patient suffered immobilizing back pain. She was readmitted to hospital 6 days after the procedure and underwent invasive investigation to exclude extradural abscess. Clearly, the value of EBP *must* be questioned if it can result in greater pain and distress than the condition it is intended to treat. (Incidentally, immobilizing back pain after EBP was first described by Cornwall and Dolan [3].)

The authors state that "severe backache after extradural block should be attributed to an extradural abscess or other serious pathological process until proved otherwise". In fact, the evidence confirms that severe backache may follow EBP *in the complete absence* of any demonstrable pathological process. Such was also the case in the patient I managed.

Two of the cardinal features of extradural abscess—pyrexia and leucocytosis [4]—were absent in the patient described and it is debatable if urgent investigation was indicated. Where there is strong suspicion of an extradural abscess, invasive radiological investigation is clearly undesirable and may be avoided if MRI scanning facilities are available.

P. C. STRIDE
Cumberland Infirmary
Carlisle

1. Seeberger MD, Urwyler A. Lumbovertebral syndrome after extradural blood patch. *British Journal of Anaesthesia* 1992; **69**: 414–416.
2. Stride PC, Cooper GM. Dural taps revisited. *Anaesthesia* 1993; (in press).
3. Cornwall RD, Dolan WM. Radicular back pain following lumbar epidural blood patch. *Anesthesiology* 1975; **43**: 692–693.
4. Hulme A, Dott NM. Spinal epidural abscess. *British Medical Journal* 1954; **1**: 64–68.

Sir,—We appreciate the interest of Dr Stride in our recent case report [1] and we share his opinion that the extradural blood patch (EBP) has some potentially serious side effects. We further agree with him that when extradural abscess is suspected, invasive radiological investigation is undesirable unless computed tomography has shown no pathological findings, as in our patient. We look forward to reading his review of experience with EBP at the Birmingham Maternity Hospital, as the surprisingly low success rate contrasts not only with our own limited experience, but also with several reports published on this topic [2–8].

However, we disagree with Dr Stride's conclusion that the value of an effective therapy introduced 31 years ago [9] and in widespread use today [10] must be questioned after three reports of painful side effects (fortunately, none of them with permanent damage). We agree that most patients with post-dural puncture headache (PDPH) do not need an EBP, but this therapy should be offered to the small percentage of patients with severe PDPH not responding to conservative treatment. Moreover, the syndrome of continued leakage of CSF after dural puncture may be complicated in rare cases by cranial nerve palsies [11], and even fatal subdural haematoma [12].

The most important point of disagreement, however, results from Dr Stride's statement that "it is debatable if urgent investigation was indicated". Many publications confirm that the extent of permanent neurological sequelae is related directly to the time required for diagnosis and surgical correction of haematomas [13–17] or abscesses [18, 19] associated with lumbar punctures. Indeed, Saady mentioned that an atypical presentation of extradural abscess may be a cause for delayed diagnosis [19]. Therefore, we reaffirm our statement that immediate investigation is warranted in any patient with immobilizing back pain after lumbar puncture.

M. D. SEEBERGER
A. URWYLER
University of California
San Francisco

1. Seeberger M, Urwyler A. Lumbovertebral syndrome after extradural blood patch. *British Journal of Anaesthesia* 1992; **69**: 414–416.
2. DiGiovanni A, Dunbar B. Epidural injection of autologous blood for postlumbar-puncture headache. *Anesthesia and Analgesia* 1970; **49**: 268–271.
3. DiGiovanni A, Galbert M, Wahle W. Epidural injection of autologous blood for postlumbar-puncture headache. II. additional clinical experiences and laboratory investigation. *Anesthesia and Analgesia* 1972; **51**: 226–232.
4. Abouleish E, Vega S, Blendinger I, Tio T. Long-term follow-up of epidural blood patch. *Anesthesia and Analgesia* 1975; **54**: 459–463.
5. Crawford J. Experiences with epidural blood patch. *Anaesthesia* 1980; **35**: 513–515.
6. Crawford J. Epidural blood patch. *Anaesthesia* 1985; **40**: 381.
7. Szeinfeld M, Ihmeidan I, Moser M, Machado R, Klose K, Serafini A. Epidural blood patch: evaluation of the volume and spread of blood injected into the epidural space. *Anesthesiology* 1986; **64**: 820–822.
8. Tarkkila P, Miralles J, Palomaki E. The subjective complications and efficiency of the epidural blood patch in the treatment of postdural puncture headache. *Regional Anesthesia* 1989; **14**: 247–250.
9. Gormley J. Treatment of post spinal headache. *Anesthesiology* 1960; **21**: 565–566.
10. Reid JA, Thorburn J. Headache after spinal anaesthesia. *British Journal of Anaesthesia* 1991; **67**: 674–677.
11. Vandam L, Dripps R. Long term follow up of patients who received 10,098 spinal anesthetics. Syndrome of decreased intracranial pressure (headache and occular and auditory difficulties). *Journal of the American Medical Association* 1956; **161**: 586–591.
12. Endelman J, Wingard D. Subdural hematomas after lumbar puncture. *Anesthesiology* 1980; **52**: 166–167.
13. Helperin S, Cohen D. Hematoma following epidural anesthesia: report of a case. *Anesthesiology* 1971; **35**: 641–644.
14. Lerner S, Gutterman P, Jenkins F. Epidural hematoma and paraplegia after numerous lumbar punctures. *Anesthesiology* 1973; **39**: 550–551.
15. Brem S, Hafler D, Uitert RV, Ruff R, Reichert W. Spinal subarachnoid hematoma. A hazard of lumbar puncture resulting in reversible paraplegia. *New England Journal of Medicine* 1981; **30**: 1020–1021.
16. Reith C. Epidural hematoma following epidural anesthesia. *Regional Anesthesie* 1989; **12**: 99–101.
17. Tekkok I, Cataltepe O, Tahta K, Bertan V. Extradural haematoma after continuous extradural anaesthesia. *British Journal of Anaesthesia* 1991; **67**: 112–115.
18. Ferguson J, Kirsch W. Epidural empyema following thoracic extradural block. *Journal of Neurosurgery* 1974; **41**: 762–764.
19. Saady A. Epidural abscess complicating thoracic epidural analgesia. *Anesthesiology* 1976; **44**: 244–246.

INTERMITTENT *VS* CONTINUOUS EXTRADURAL INFUSION OF BUPIVACAINE DURING LABOUR

Sir,—The absolute significance of the findings of Eddleston and colleagues [1] would have been much clearer if they had compared the two extradural groups with a control group which did not receive extradural bupivacaine. Although this control group would have been self-selected and not subject to randomization, the group could have been matched as closely as possible to the two study groups.

In addition, although the incidence of oxytocin use was recorded in this study, an analysis of the association between oxytocin use and the fetal heart rate abnormalities would have provided additional information. This association is recognized widely, and ascribing heart rate abnormalities to different extradural techniques irrespective of the use of oxytocin may not be valid.

Whilst it is tempting to attribute fetal heart rate abnormalities to uptake of bupivacaine by the fetal myocardium, the evidence for this is far from conclusive. Although Abboud and colleagues [2] also observed fetal heart rate abnormalities after extradural bupivacaine, other factors may have been contributory. In the large majority of cases, abnormalities are associated with aorto-caval compression which is not always diagnosed or recognized [3]. The umbilical vein:maternal vein concentration ratio of bupivacaine is only an index of placental transfer in that it describes the equilibrium concentration ratio of bupivacaine across the placenta at one moment in time. Although Kuhnert and colleagues [4] suggested that low fetal: material ratios were caused by extensive fetal tissue uptake, more recent work in animals by Laishley, Carson and Reynolds [5] does not support this. In our study, in the presence of a constant maternal arterial concentration of bupivacaine, fetal plasma and brain concentrations increased slowly over 120 min and only approached a fetal:maternal ratio of 0.3 at that time. Moreover, despite bupivacaine being lipophilic, the fetal brain:fetal blood concentration ratio diminished over this time. This latter finding indicates that there is not extensive tissue uptake by fetal brain.

The predominant reason for the low fetal:maternal ratio of bupivacaine is the difference in concentration in alpha$_1$-acid glycoprotein across the placenta, and the resulting relative difference in the proportion of bupivacaine bound to glycoprotein [6]. Moreover, fetal acidosis, which may be associated with the use of oxytocin, promotes placental transfer of bupivacaine by ion trapping of the basic drug [7]. The study by Reynolds and colleagues [8] confirmed the relatively small fetal plasma concentration of bupivacaine (umbilical samples at delivery) after a large bolus dose of extradural bupivacaine for Caesarean section. If it is hypothesized that bupivacaine causes fetal myocardial toxicity in these small concentrations, then it suggests that the fetal myocardium is much more sensitive than adult myocardium.

Finally, the conclusion of Eddleston and colleagues [1] that there is no advantage in either extradural intermittent bolus or infusion techniques ignores the fact that the infusion technique may be safer. A survey of the Reports on Confidential Enquiries into Maternal Deaths between 1970 and 1987 [9] reveals that four of the 10 deaths directly associated with extradural analgesia were caused by total spinal anaesthesia and extradural bolus doses of bupivacaine. So far, there are no descriptions in these reports [9] of any death associated with an extradural infusion.

R. S. Laishley
Ealing Hospital
London

1. Eddleston JM, Maresh M, Horsman EL, Young H, Lacey P, Anderton J. Comparison of the maternal and fetal effects associated with intermittent or continuous infusion of extradural analgesia. *British Journal of Anaesthesia* 1992; **69**: 154–158.
2. Abboud TK, Khoo SS, Miller F, Doan T, Henriksen EH. Maternal, fetal and neonatal responses after epidural anesthesia with bupivacaine, 2-chloroprocaine, or lidocaine. *Anesthesia and Analgesia* 1982; **61**: 638–644.
3. Kinsella SM, Whitwam JG, Spencer JAD. Reducing aorto-caval compression; how much tilt is enough? *British Medical Journal* 1992; **305**: 539–540.
4. Kuhnert PM, Kuhnert BR, Stitts JM, Gross TL. The use of a selected ion monitoring technique to study the disposition of bupivacaine in mother, fetus, and neonate following epidural anesthesia for Cesarean section. *Anesthesiology* 1981; **55**: 611–617.
5. Laishley RS, Carson RJ, Reynolds F. Effects of adrenaline on the distribution of bupivacaine in the rabbit fetus. *British Journal of Anaesthesia* 1989; **63**: 721–725.
6. Petersen MC, Moore RG, Nation RL, McMeniman W. Relationship between the transplacental gradients of bupivacaine and alpha-1-acid glypoprotein. *British Journal of Pharmacology* 1981; **12**: 859–862.
7. Kennedy RL, Erenberg A, Robillard JE, Merkow A, Turner T. Effects of changes in maternal–fetal pH on the transplacental equilibrium of bupivacaine. *Anesthesiology* 1979; **51**: 50–54.
8. Reynolds F, Laishley R, Morgan B, Lee A. Effect of time and adrenaline on the feto–maternal distribution of bupivacaine. *British Journal of Anaesthesia* 1989; **62**: 509–514.
9. Department of Health and Social Security. *Reports on Confidential Enquiries into Maternal Deaths 1970–72; 1973–75; 1976–78; 1979–81; 1982–84; 1985–87.* London: Her Majesty's Stationery Office.

Sir,—Thank you for the opportunity of replying to Dr Laishley's detailed letter. Our study was an attempt to examine, in particular, the potential effects on the fetus of extradural analgesia with bupivacaine. Exhaustive studies comparing intermittent and continuous infusion extradural analgesia with bupivacaine failed to demonstrate any maternal advantage associated with either regimen [1, 2]. To date, no attention has been paid to the effect of the two regimens on the fetus, in particular fetal heart rate pattern. In our study, we documented 71 deceleratory episodes in the intermittent group and 69 in the infusion group. We found no difference between groups in the incidence of deceleration occurring within 30 min of an extradural top-up, but we did detect a discrepancy in its severity and duration. In the intermittent group, the majority of decelerations (73.8%) were recorded as transient, whereas in the infusion group 61.1% of episodes lasted in excess of 10 min.

Indeed, there are several other potential causes for fetal heart rate decelerations, including aortocaval compression producing hypotension, the use of oxytocics and fetal acidosis, all of which are referred to in Dr Laishley's letter. I can restate that none of the deceleratory episodes referred to in our paper occurred in the presence of maternal upper limb hypotension. Obviously, this does not exclude the presence of concealed aortocaval compression. In addition, there was no difference in the mean dose of oxytocic required by each treatment group or in the acid–base status of the two groups at delivery.

Finally, we accept Dr Laishley's comments concerning a control group. Such a group almost universally would have received another form of analgesia, most probably parenteral pethidine. We do not feel that this could be described as a control group.

In conclusion, we wish to restate that there is no advantage to either mother or fetus in using an extradural infusion of 0.125% bupivacaine compared with intermittent injections of 0.25% bupivacaine. We accept, however, that the infusion technique should, in theory, be less likely to produce total spinal anaesthesia in the case of a misplaced extradural catheter.

J. M. Eddleston
Manchester Royal Infirmary
Manchester

1. Smedstad KG, Morrison DH. A comparative study of continuous and intermittent epidural analgesia for labour and delivery. *Canadian Journal of Anaesthesia* 1988; **35**: 234–241.
2. Bogod DG, Rosen N, Rees GAD. Extradural infusion of 0.125% bupivacaine at 10 ml h^{-1} to women during labour. *British Journal of Anaesthesia* 1987; **59**: 325–330.

DOES ETOMIDATE CAUSE HAEMOLYSIS?

Sir,—I read with interest the article "Does etomidate cause haemolysis?" by Nebauer and colleagues [1], as it reminded me of an unreported finding after etomidate use in domestic cats. We conducted research several years ago at the Veterinary Teaching Hospital at the University of Illinois to determine the anaesthetic effects and pharmacokinetics of etomidate in domestic cats [2, 3]. We used Amidate i.v. (Abbott Laboratories) in a dose of 3 mg kg^{-1}

(this dose is 10 times greater than the dose reportedly used in man). In our study, multiple samples of venous blood were obtained from each cat for analysis of the plasma concentration of etomidate (2.5 min to 12 h). All blood samples were haemolysed. This did not interfere with the analyses, but was of interest. I am sure that the haemolysis was more obvious to us because of the greater dose used.

As was mentioned in the article, etomidate is prepared with a propylene glycol base (35 vol %). It has been reported previously that propylene glycol does indeed cause haemolysis [4]. Thus haemolysis occurring in man is most likely to be produced by the vehicle.

E. Wertz
Veterinary Teaching Hospital
Fort Collins, Colorado

1. Nebauer AE, Doenicke A, Hoernicke R, Angster R, Mayer M. Does etomidate cause haemolysis? *British Journal of Anaesthesia* 1992; **69**: 58–60.
2. Wertz EM, Benson GJ, Thurmon JC, Tranquilli WJ, Davis LE, Koritz GD. Pharmacokinetics of etomidate in cats. *American Journal of Veterinary Research* 1990; **51**: 281–285.
3. Wertz EM. Pharmacokinetic modeling and assessment of anesthetic response of cats receiving intravenous thiamylal or etomidate. Master's Thesis, University of Illinois, 1986.
4. Gross DR, Kitzman JV, Adams HR. Cardiovascular effects of intravenous administration of propylene glycol and of oxytetracycline in propylene glycol in calves. *American Journal of Veterinary Research* 1979; **40**: 783–791.

Sir,—We read with interest the letter of Dr Wertz reporting haemolysis in cats after the use of etomidate dissolved in propylene glycol (PG). In reviewing the literature we had also found a report on PG-induced Heinz body formation, change in membrane deformability, reduced erythrocyte survival and haemolysis in cats fed with PG-containing pet food. Also, *in vitro* tests caused haemolysis of red blood cells [1].

We decided not to refer to these observations in our article because feline erythrocytes differ from human red blood cells and appear to be more susceptible to damage. However, we do now wish to refer to an article by Molter and colleagues [2], who reported haemolysis, *in vitro* and *in vivo*, using etomidate dissolved in 45 vol % PG.

Whether haemolysis is caused by hyperosmolality of the solution, by a direct effect of PG on cell membranes, or both, has to be investigated further. In conclusion, all authors have suggested re-evaluation of the safety of propylene glycol, especially in large concentrations and when administered over a prolonged time.

A. Doenicke
A. E. Nebauer
R. Hoernecke
R. Angster
M. Mayer
Institut für Anaesthesiologie
LMU, München

1. Christopher MM, Perman V, White JG, Eaton JW. Propylene glycol-induced Heinz body formation and D-lactic acidosis in cats. *Progress in Clinical and Biological Research* 1989; **319**: 69–92.
2. Molter K, Lieb L, Fiedler H, Zimmermann K. Serum-hyperosmolalität bei Langzeitanwendung von Etomidate (Radenarcon). *Anaesthesiologie und Reanimation* 1987; **12**: 25–34.

XYLOMETAZOLINE AND PORPHYRIA

Sir,—A 45-yr-old female who had variegate porphyria diagnosed in 1979 presented for submucous resection of the nose. Several previous anaesthetics had made her feel unwell. Symptoms included blistering of the skin, depression and abdominal and joint pain. She was prescribed β carotene.

She did not receive any premedication. Anaesthesia was induced and maintained with propofol (total dose 300 mg), fentanyl 0.05 mg and 60 % nitrous oxide in oxygen, administered via a laryngeal mask and a Bain coaxial circuit. An adrenaline nasal pack inserted in the ward was removed before surgery and local anaesthesia was not used. Anaesthesia and recovery were uneventful.

Urine samples collected for 24 h before, and 24 h and 48 h after operation were screened for porphyrins (table I).

TABLE I. *Urinary porphyrin concentrations*

	Porphobilinogen (μmol/24 h)	Total porphyrin (nmol/24 h)
Reference values	0–12	0–320
Before anaesthesia	6.39	215
After anaesthesia		
24 h	7.80	430
48 h	19.86	475

The results revealed normal concentrations of porphyrins before operation. Xylometazoline (Otrivine) nasal spray was used 20 h after operation and was the only drug associated with the increase in porphobilinogen concentration. Xylometazoline has been advocated as a safe alternative to other vasoconstrictors and is used commonly in nasal surgery. It may be advisable to avoid its use in porphyric patients.

N. D. Platt
Princess Alexandra Hospital
Wroughton

TRANSTHORACIC ENDOSCOPIC SYMPATHECTOMY

Sir,—We read with interest the recent article on transthoracic endoscopic sympathectomy for upper limb hyperhidrosis [1]. We have used this technique in three patients and agree with the observation that postoperative pain is mainly retrosternal, but in our patients this lasted for more than 12 h. We postulate that this was the result of manipulation and displacement of the mediastinum during carbon dioxide insufflation and subsequent one-lung anaesthesia. There was minimal discomfort from the puncture sites. We have provided analgesia via intrapleural catheters in all our patients, two of whom had bilateral procedures.

The catheters were introduced by the surgeon under direct vision through one of the endoscopy ports before reinflation of the lung. The catheter was placed at the apex of the lung in the vicinity of the operation site. Postoperative analgesia was achieved in all our patients with 0.25 % bupivacaine 20 ml, given via one or both catheters in recovery, and repeated 4 and 12 h later. A second advantage of intrapleural catheters has been the ability to extract any residual pneumothorax.

Our experience includes bilateral procedures and sequential lung collapse. We have noted periods of arterial desaturation during one-lung anaesthesia on the second side. We feel that there is a significant period of time after reinflation of the first lung when pulmonary physiology is inadequate to sustain oxygenation on that lung.

S. Gilligan
M. B. Smith
P. R. Allen
Royal Lancaster Infirmary
Lancaster

1. Jedeikin R, Olsfanger D, Shachor D, Mansoor K. Anaesthesia for transthoracic endoscopic sympathectomy in the treatment of upper limb hyperhidrosis. *British Journal of Anaesthesia* 1992; **69**: 349–351.

Sir,—We thank Drs Gilligan, Smith and Allen for their comments on our recent article [1].

Nearly all our patients experienced pain during the first 4 h after surgery, unless there was any complication (pneumothorax, haemothorax or the need for a thoracic drain). This retrosternal or upper back pain was controlled with a combination of preoperative midazolam and fentanyl, with an additional postoperative i.v. or i.m. dose of opioid titrated to the individual patient's needs. We were reluctant to use intrapleural analgesia administered via a catheter inserted through the endoscope because of the possible danger of bilateral phrenic nerve block [2].

It is unnecessary to leave a catheter in the pleural cavity to treat a residual pneumothorax, as this can be avoided by reinflating the lungs under direct vision until they are seen to bulge into the lumen of the endoscope. We are of the opinion that such a catheter would complicate the procedure and increase the duration of stay in hospital. Patients lacking complications were discharged from hospital after 12–24 h.

We did not compare the incidence of arterial desaturation between the first and second side. We discussed in our article the possible mechanism of this desaturation. In practice, after it had been checked that there was no endobronchial tube misplacement, the arterial desaturation immediately improved with one or two small manual ventilations of the collapsed lung. This manoeuvre does not disturb the surgeon and we would suggest that the arterial desaturation is related to the degree of lung collapse [3].

R. Jedeikin
D. Olsfanger
D. Shachor
K. Mansoor
Meir Hospital
Kfar Saba, Israel

1. Jedeikin R, Olsfanger D, Shachor D, Mansoor K. Anaesthesia for transthoracic endoscopic sympathectomy in the treatment of upper limb hyperhidrosis. *British Journal of Anaesthesia* 1992; **69**: 349–351.
2. Ahlburg P, Molgaard J, Rasmussen BS, Noreng MF. Intrapleural administration of 0.5% plain bupivacaine compared to 0.5% epinephrine: a hemodynamic and ventilatory study. *Regional Anesthesia* 1991; **16**: 257–261.
3. Marshall BE, Marshall C. Continuity of response to hypoxic pulmonary vasoconstriction. *Journal of Applied Physiology* 1980; **49**: 189–196.

Sir,—We read with interest the article by Jedeikin and colleagues on anaesthesia for transthoracic sympathectomy as treatment for upper limb hyperhidrosis [1, 2]. They reported that 56 of their 58 patients experienced distressing retrosternal or upper back pain during the first 2–4 h after operation. Recently, we have anaesthetized six patients for this procedure in our hospital and have found that intrapleural 0.5% bupivacaine introduced immediately before removal of the last endoscopic port provided excellent postoperative pain relief. As far as we are aware, this technique has not been described previously [3–6].

Whereas 43 of Dr Jedeikin's 58 patients had bilateral sympathectomies, all of our patients had unilateral procedures. In most respects, the anaesthetic techniques were similar. Our patients received either no premedication or a benzodiazepine. Induction was with thiopentone 3–5 mg kg^{-1}. Intubation and intermittent positive pressure ventilation were facilitated with vecuronium 0.1 mg kg^{-1}. All patients had the trachea intubated with left-sided Robertshaw endobronchial tubes and anaesthesia was maintained with enflurane in oxygen–nitrous oxide supplemented with either papaveretum 0.2 mg kg^{-1} or alfentanil 0.1 mg kg^{-1}. At the end of the procedure, 0.5% bupivacaine 2 mg kg^{-1} was instilled intrapleurally. No intrapleural drains were left *in situ*.

All patients were comfortable in the recovery ward, the worst pain being described as a dull ache in the ipsilateral arm and relieved by paracetamol. No toxic effects of bupivacaine were seen [7] and all patients were discharged from hospital within 24 h.

From our limited experience, it would seem that this technique provides effective pain relief for the procedure of transthoracic endoscopic sympathectomy.

S. E. Plastow
M. T. Weisz
St Mary's Hospital
London

1. Jedeikin R, Olsfanger D, Shacher D, Mansoor K. Anaesthesia for transthoracic endoscopic sympathectomy in the treatment of upper limb hyperhidrosis. *British Journal of Anaesthesia* 1992; **69**: 349–351.
2. Byrne J, Walsh TN, Hederman WP. Endoscopic transthoracic electrocautery of the sympathetic chain for palmar and axillary hyperhidrosis. *British Journal of Surgery* 1990; **77**: 1040–1049.
3. Reiestad F, Stomskag KE. Interpleural catheter in the management of postoperative pain, a preliminary report. *Regional Anesthesia* 1986; **11**: 89–91.
4. Durrani Z, Winnie AP, Ikuta P. Interpleural catheter analgesia for pancreatic pain. *Anesthesia and Analgesia* 1988; **67**: 479–481.
5. Reiestad F, McIlvaine WB. Interpleural anesthesia for extracorporeal shock wave lithotripsy. *Anesthesia and Analgesia* 1989; **69**: 551–552.
6. Rosenberg PH, Scheinin BM-A, Lepäntalo MJA, Lindfors O. Continuous intrapleural infusion of bupivacaine for analgesia after thoracotomy. *Anesthesiology* 1987; **67**: 811–813.
7. El-Baz N, Penfield Faber L, Ivankovich AD. Intrapleural infusion of local anesthetic: A word of caution. *Anesthesiology* 1988; **68**: 809–810.

PERIOPERATIVE BLOOD LOSS

Sir,—The review by Dr Simpson on perioperative blood loss and its reduction was most interesting [1]. As the level of concern about transfusion-related infection has increased greatly in the past decade, so has interest in means of reducing requirements for blood products. The other reason for reducing intraoperative bleeding is to facilitate surgery by providing a bloodless field. However, the article did not include some of the most recent techniques available to the anaesthetist to decrease blood loss.

Normovolaemic haemodilution is used often to decrease the need for transfusion of homologous blood. The technique is safe and effective as long as rigorous criteria are followed [2]. The technique also offers several advantages such as increased cardiac output, better regional blood flow and better tissue perfusion. The practical aspects, physiological consequences and inclusion criteria of the technique have been reviewed recently [3].

Specific pharmacological agents have been used to decrease blood loss. They are used more commonly during operations in which massive blood loss is anticipated, such as during cardiac surgery and orthotopic liver transplantation. An impressive reduction in both intraoperative and postoperative blood loss was reported after the use of high dose aprotinin during cardiac surgery [4]. Aprotinin (Trasylol) is a serine protease inhibitor known to inhibit human plasmin, trypsin and tissue kallikrein. It is postulated that aprotinin prevents the activation of plasma proteins and platelets during cardiopulmonary bypass, and thereby helps to preserve normal coagulation. Aprotinin has been used successfully for the reduction of blood loss after liver transplantation [5] and peripheral vascular surgery [6]. Synthetic and natural antifibrinolytic agents have been used to decrease bleeding after cardiac surgery.

Desmopressin, a synthetic form of the hormone vasopressin which releases factor VIII and von Willebrand's factor from endogenous sites, has been used to reduce bleeding during major orthopaedic surgery [7] and complicated valvular surgery [8]. Tranexamic acid [9] and ε-aminocaproic acid [10] have been shown to decrease postoperative bleeding after cardiopulmonary bypass. However, the initial reports concerning these agents have not been substantiated and their use during surgery is much debated.

A variety of techniques can aid the anaesthetist in reducing perioperative blood loss, but the clinician must weigh the benefits and disadvantages of these intraoperative techniques in each patient before deciding to use any one.

B. Appadu
Leicester Royal Infirmary
Leicester

1. Simpson P. Perioperative blood loss and its reduction: the role of the anaesthetist. *British Journal of Anaesthesia* 1992; **69**: 498–507.
2. Messmer K. Haemodilution—possibilities and safety aspects. *Acta Anaesthesiologica Scandinavica* 1988; **32**: S49–53.
3. Côté DJ. L'hémodilution normovolémique. *Canadian Journal of Anaesthesia* 1991; **38**: 243–251.
4. Bidstrup BP, Royston D, Sapsford RN, Taylor KM. Reduction in blood loss and blood use after cardiopulmonary bypass with high dose aprotinin (trasylol). *Journal of Thoracic and Cardiovascular Surgery* 1989; **97**: 364–372.

5. Mallett SV, Rolles K, Cox D, Burroughs A, Hunt B. Intraoperative use of aprotinin (Trasylol) in orthotopic liver transplantation. *Transplantation Proceedings* 1991; **23**: 1931–1932.
6. Thomson JF, Roath OS, Francis JL, Webster JHM, Chant ADB. Aprotinin in peripheral vascular surgery. *Lancet* 1990; **335**: 911.
7. Kobrinsky NL, Letts MR, Patel LR, 1-Desamino-8-D arginine vasopressine (Desmopressin) decreases operative blood loss in patients having Harrington rod spinal fusion surgery. *Annals of Internal Medicine* 1987; **107**: 446–450.
8. Salzmann EW, Weinstein MJ, Weintraub RM, Ware JA, Thurer RL, Robertson RL, Donovan A, Gaffney T, Bertele V, Troll J, Smith M, Chute LE. Treatment with desmopressin acetate to reduce blood loss after cardiac surgery. *New England Journal of Medicine* 1986; **314**: 1402–1406.
9. Horrow JC, Van Riper DF, Strong MD, Brodsky I, Parmet J. The hemostatic effects of tranexamic acid, and desmopressin during cardiac surgery. *Circulation* 1991; **84**: 2063–2070.
10. Stems LP, Lillehei CW. Effect of epsilon-aminocaproic acid upon blood loss following open-heart surgery: an analysis of 340 patients. *Canadian Journal of Surgery* 1967; **10**: 304–307.

It should be noted that Dr Simpson's review on perioperative blood loss was commissioned originally as part of a Postgraduate Educational issue, devoted to various aspects of haematology. Some 10–11 articles were commissioned and some of these would have dealt in great detail with the other methods of decreasing blood loss, referred to above by Dr Appadu. Unfortunately, however, most of these reviews failed to materialize and it was not possible to produce a single issue. Thus Dr Simpson's article covered only the area requested of him by the Editor of Educational Reviews.

GRAHAM SMITH
Editor

PRE-EMPTIVE EXTRADURAL ANALGESIA

Sir,—In their letter, Dr Wilder-Smith and colleagues [1] ask an important question which neither they nor the replying letter [2] address. Why do yet further studies fail "to produce the results expected from previous experimental work [3]" in relation to pre-emptive analgesia?

This previous experimental work with the concept of "pre-emptive analgesia" and related concepts such as "wind-up" were derived in neurophysiological laboratories in which stimuli are applied to (often neonatal and often decerebrate) animal spinal cord preparations [4], and responses such as the electrical output of neurones including ventral horn (motor) cells [4] measured. In order to obtain the so-called pre-emptive analgesia in rats "low-dose" morphine (0.5 $mg\ kg^{-1}$) is used, as opposed to larger doses (5 $mg\ kg^{-1}$) needed to suppress this effect when the drug is given after the stimulus [5]. Such industrial doses have no relevance to clinical practice. The phenomenon of wind-up lasts only a few minutes [6] compared with the pain response after injury, which lasts for days. Discussion about the comparative actions of lignocaine or bupivacaine are irrelevant, as there are no comparative studies.

In the clinical studies of extradural analgesia [7, 8] and peripheral neural block [9], the pain report of conscious man is measured after standard surgical insults. The two experimental systems are assessing totally unrelated events—what would be an even greater surprise would be for there to be any correlation between the two, not that there is a lack of correlation. To answer the question as posed, the studies of analgesia in man "fail to reproduce previous experimental work" because that work was not the study of pain or the response of analgesics in man. Pain is not just nociception. It is *only* by the study of pain and pain mechanisms in man that there will be any advances in clinical practice.

P. A. J. HARDY
Gloucestershire Royal Hospital
Gloucester

1. Wilder-Smith OHG, Borgeat A, Tramer M, Morel DR. Pre-emptive extradural analgesia. *British Journal of Anaesthesia* 1992; **69**: 663–664.
2. Dahl JB, Hansen BL, Hjortsø N-C, Erichsen CJ, Møiniche S, Kehlet H. Pre-emptive extradural analgesia. *British Journal of Anaesthesia* 1992; **69**: 664–665.
3. Woolf CJ. Recent advances in the pathophysiology of acute pain. *British Journal of Anaesthesia* 1989; **63**: 139–146.
4. Wilcox GL. Role of central changes in secondary hyperalgesia: Discussion. In: Willis WD, ed. *Hyperalgesia and Allodynia*. New York: Raven Press, 1991; 261.
5. Woolf CJ. Excitability changes in central neurons following peripheral damage. Role of central sensitization in the pathogenesis of pain. In: Willis WD, ed. *Hyperalgesia and Allodynia*. New York: Raven Press, 1991; 221–243.
6. Haley JE, Wilcox GL. Involvement of excitatory amino acids and peptides in the spinal mechanisms underlying hyperalgesia. In: Willis WD, ed. *Hyperalgesia and Allodynia*. New York: Raven Press, 1991; 281–293.
7. Dahl JB, Hansen BL, Hjortsø N-C, Erichsen CJ, Møiniche S, Kehlet H. Influence of timing on the effect of continuous extradural analgesia with bupivacaine and morphine after major abdominal surgery. *British Journal of Anaesthesia* 1992; **69**: 4–8.
8. Pryle BJ, Vanner R, Enriquez N, Reynolds F. Can preemptive epidural blockade reduce postoperative pain following lower abdominal surgery? *Anaesthesia* 1993; (in press).
9. Dierking G, Dahl JB, Kanstrup J, Dahl A, Kehlet H. The effect of pre *vs* postoperative inguinal field block on postoperative pain following herniorrhaphy. *British Journal of Anaesthesia* 1992; **68**: 344–348.

METABOLIC EFFECTS OF CHOLECYSTECTOMY

Sir,—We read with interest the study of Joris and colleagues [1] comparing the metabolic and respiratory changes after standard and laparoscopic cholecystectomy. We have compared the same variables after minilaparotomy and laparoscopic cholecystectomy as part of a prospective, randomized controlled trial. In our study, after laparoscopic cholecystectomy there were better postoperative pulmonary function and oxygen saturation, and lower pain scores and morphine consumption using a patient-controlled analgesia device than after a minilaparotomy cholecystectomy [2–4]. In these respects, our findings are in agreement with those of Joris and colleagues.

However, our findings on the metabolic response to surgery after the two procedures (10 patients in each group) [5] differ significantly. Serum C reactive protein (CRP) was measured by nephelometry, while serum interleukin-6 (IL-6) was measured using a hybridoma growth stimulation assay. Values were (means (SEM)): CRP at 48 h—laparoscopy 118 (50) $mg\ litre^{-1}$, minilaparotomy 122 (30) $mg\ litre^{-1}$; IL-6 at 24 h—laparoscopy 227 (41) $pg\ ml^{-1}$, minilaparotomy 252 (46) $pg\ ml^{-1}$.

In our study, there was a wide variation in the metabolic response within groups, but there was no significant difference between the two groups. As a result of a different assay technique, our IL-6 results are substantially greater and cannot be compared directly with those of Joris and colleagues. Furthermore, in our study, the CRP response after laparoscopic cholecystectomy was more than twice that found by Joris and colleagues. Given that there is wide variation in the magnitude of the metabolic response to surgery, it is not surprising that studies with small patient numbers can produce such different results. In the study of Joris and colleagues, patients were not allocated randomly to groups. Patient selection bias may, therefore, account for the difference in findings.

A. J. MCMAHON
J. N. BAXTER
P. J. O'DWYER
Western Infirmary
Glasgow

1. Joris J, Cigarini I, Legrand M, Jacquet N, De Groote D, Franchimont P, Lamy M. Metabolic and respiratory changes after cholecystectomy performed via laparotomy or laparoscopy. *British Journal of Anaesthesia* 1992; **69**: 341–345.
2. McMahon AJ, Baxter JN, Anderson JR, Ramsay G, Galloway D, Russell IT, O'Dwyer PJ. Assessment of pain after

laparoscopic and minilap cholecystectomy: a randomised trial. *British Journal of Surgery* 1992; **79**: 1224.

3. McMahon AJ, Baxter JN, Anderson JR, Ramsay G, Galloway D, Russell IT, O'Dwyer PJ. Pulmonary function after laparoscopic and minilap cholecystectomy: a randomised trial. *British Journal of Surgery* 1992; **79**: 1226.
4. McMahon AJ, Baxter JN, Anderson JR, Ramsay G, Galloway D, Sunderland G, Russell IT, O'Dwyer PJ. Post-operative pain and analgesia requirement after laparoscopic and minilap cholecystectomy: a prospective randomised trial. *Gut* 1992; **33**: S63.
5. McMahon AJ, O'Dwyer PJ, McMillan D, Cruikshank A, Lowe G, Rumley A, O'Reilly D, Logan R, Baxter JN. Does the laparoscopic method result in a reduced metabolic response to surgery? *Irish Journal of Medical Science* 1992; **161** (Suppl. 11): 39.

Sir,—We appreciate the interest of McMahon and colleagues in our work [1] on the metabolic and respiratory changes after standard and laparoscopic cholecystectomy. Using randomized studies, Putensen and colleagues [2] and McMahon and colleagues [3, 4] confirmed better postoperative pulmonary function, greater Sp_{O_2} and smaller pain scores, opioid consumption, or both, after laparoscopic cholecystectomy than after open cholecystectomy as demonstrated in our article.

Laparoscopic cholecystectomy avoids a large abdominal incision and attendant retraction. Furthermore, gall bladder dissection "appears" less traumatic, less extensive and more precise during laparoscopy. The reported benefits of laparoscopy on postoperative pulmonary function and pain were therefore expected and, for us, were related mainly to reduction of surgical trauma. We measured C-reactive protein (CRP) and IL-6 to document objectively the reduction in tissue injury. Increases in plasma concentrations of IL-6 and CRP, considered as indicators of the amount of tissue damage [5, 6] were significantly less after laparoscopy. McMahon and colleagues [7], however, could not find any significant difference between laparoscopic and open cholecystectomy.

We do not think that patient selection bias accounts for the discrepancies between the findings of their randomized study, and ours which was not randomized. First, our study was carried out early after the introduction of laparoscopic cholecystectomy. All the patients in our study were operated on by experienced senior surgeons, more acquainted with the technique of open than laparoscopic cholecystectomy. We suspect, therefore, that the difference reported in our study would be even greater if the comparisons were to be made now, 2 years later. Second, although the study was carried out shortly after the introduction of laparoscopic cholecystectomy, by the time we decided to undertake it, open cholecystectomies were no longer performed in our hospital except for acute cholecystitis or complicated cases. A randomized, controlled study of open *vs* laparoscopic cholecystectomy was not appropriate when our study was designed and, I regret, will no longer be possible in the light of the multiple benefits favouring the laparoscopic approach [8]. We therefore used historical controls [1].

We also noticed a wide within-group variation for CRP (measured by nephelometry), but this was still five times less than that of McMahon and colleagues. Serum concentrations of CRP in their study were very great. The mean concentrations of CRP in our study were in the range reported in other studies [9, 10]. As far as IL-6 is concerned, we used a radioimmunometric assay, whereas McMahon's group used a bioassay; comparison of the two sets of data for IL-6 is therefore difficult. However, Jakeways and colleagues [11], using a bioassay, also reported peak plasma concentrations of IL-6 and CRP significantly greater after laparotomy than after laparoscopy. Moreover, peak plasma concentrations of IL-6 and CRP correlated well in our study. Therefore, as our findings were expected and confirmed clinical observation, we consider our data valid.

J. Joris
Centre Hospitalier Universitaire
Liège

1. Joris J, Cigarini I, Legrand M, Jacquet N, De Groote D, Franchimont P, Lamy M. Metabolic and respiratory changes after cholecystectomy performed via laparotomy or laparoscopy. *British Journal of Anaesthesia* 1992; **69**: 341–345.
2. Putensen-Himmer G, Putensen C, Lammer H, Lingnan W, Aigner F, Benzer H. Comparison of postoperative respiratory function after laparoscopy or open laparotomy for cholecystectomy. *Anesthesiology* 1992; **77**: 675–680.
3. McMahon AJ, Baxter JN, Anderson JR, Ramsay G, Galloway D, Russel M, O'Dwyer PJ. Assessment of pain after laparoscopic and minilap cholecystectomy: a randomized trial. *British Journal of Surgery* 1992; **79**: 1224.
4. McMahon AJ, Baxter JN, Anderson JR, Ramsay G, Galloway D, Russel M, O'Dwyer PJ. Pulmonary function after laparoscopic and minilap cholecystectomy: a randomized trial. *British Journal of Surgery* 1992; **79**: 1226.
5. Stahl W. Acute phase protein response to tissue injury. *Critical Care Medicine* 1987; **5**: 545–550.
6. Heinrich CA, Cannon JG, Wolff JM. Interleukin-6 and the acute phase response. *Biochemical Journal* 1990; **265**: 621–636.
7. McMahon AJ, O'Dwyer PJ, McMillan D, Cruikshank A, Lowe G, Rumley A, O'Reilly D, Logan R, Baxter JN. Does the laparoscopic method result in a reduced metabolic response to surgery? *Irish Journal of Medical Science* 1992; **161** (Suppl. 1): 39.
8. Neugebauer E, Troidl H, Spangenberger W, Dietrich A, Lefering G. Conventional versus laparoscopic cholecystectomy and the randomized controlled trial. *British Journal of Surgery* 1991; **78**: 150–154.
9. Nishimoto N, Yoshizaki K, Tagoh H, Monden M, Kishimoto S, Hirano T, Kishimoto T. Elevation of serum interleukin-6 prior to acute phase proteins on the inflammation by surgical operation. *Clinical Immunopathology* 1989; **50**: 399–401.
10. Joris J, Cigarini I, Kamel M, Vrind Y, De Groote D, Franchimont P, Jacquet N, Lamy M. Comparison of the effects of continuous interpleural analgesia and intramuscular opiate PRN on pain metabolic response after cholecystectomy. *Regional Anaesthesia* 1991; **15**: 6.
11. Jakeways MSR, Mitchell V, Hashim IA, Chadwick SJD, Anderson J, Carli F, Shenkin A. Metabolic and inflammatory changes following laparoscopic cholecystectomy. *Proceedings of the Nutrition Society* 1993; (in press).

ERRATUM

British Journal of Anaesthesia 1993; **70**: 17–21

Equation (7) should read: $\mathrm{d}t = \mathrm{d}\theta/2\pi f$

In the equation after equation (8) the right hand side should begin, not $(k\dot{v}/2\pi f)$, but $(k\dot{v}^2/2\pi f)$.

UNIVERSITY OF LEEDS

ACADEMIC UNIT OF ANAESTHESIA

A Revision Course for the Part 3 FRCA Examination

To be held at St. James's University Hospital, Leeds
10th-14th May, 1993 inclusive

This is an intensive five-day course intended for candidates about to enter the Part 3 examination. The course consists of lectures, tutorials and clinical teaching covering those aspects most relevant to the examination. Sessions on examination technique will cover essay writing, MCQs, clinical and oral examinations.

Fee £300.00. (accommodation extra)

Early application is advised as places are limited

For further information and an application form, please contact:

Academic Unit of Anaesthesia
St. James's University Hospital,
Leeds LS9 7TF.

Telephone: 0532 836972

National Guard King Khalid Hospital, Jeddah, Saudi Arabia

International Hospitals Group has provided British management at this prestigious 340 bed hospital, since 1981 and is justly proud of its excellent reputation for high standards. Jeddah is a fascinating cosmopolitan city which combines both Western and Middle Eastern ways of life. Located in the Western province and situated on the Red Sea coast it is also the Kingdom's commercial centre.

Consultant Anaesthetist

£51,720 p.a.Tax Free

The department in our busy modern hospital has a complete and varied surgical, obstetrics, general and intensive care work load which includes major neonatal and paediatric surgery. Candidates will be expected to have held a NHS Consultant post or equivalent following completion of higher professional training.

We offer excellent benefits which include:

★ 49 days Annual Leave ★ Free Flights Every Six Months for Self, Spouse and up to 3 Dependent Children
★ Education Allowance for up to 2 Dependent Children
★ Free Accommodation and Utilities
★ Free Expatriate Financial Advice Service

Please address your application to
Professor Sir Gordon Robson CBE,
Chairman of the Medical Advisory Group, IHG
at the address below:

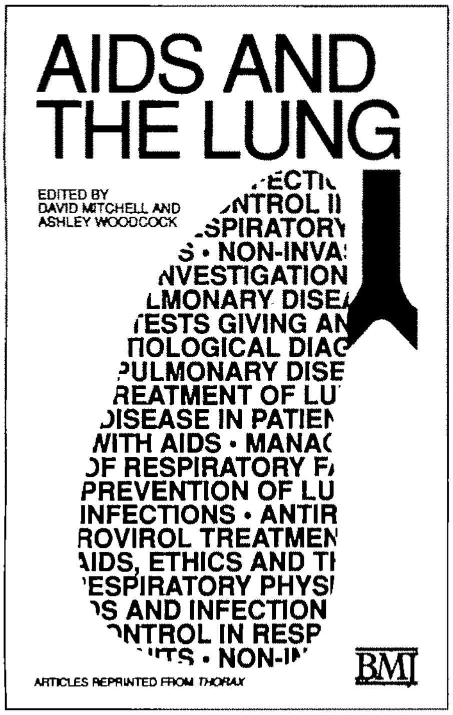
IA6249

Salary based on 5.8 SR to £1 sterling

Stoke Park.
Stoke Poges, Slough.
Berks. SL2 4NS

IHG

Telephone 0753 573222


AIDS AND THE LUNG
EDITED BY DAVID MITCHELL AND ASHLEY WOODCOCK
ARTICLES REPRINTED FROM THORAX
BMJ

"This book is a beauty!

I found it interesting and it answered many questions I had on the respiratory consequences of AIDS—plus many I wouldn't have even thought of. This book has great value for all practitioners (from medical students to specialists) who deal with AIDS and the lung."
The Medical Journal of Australia

In *AIDS and the lung* experts review the problems, emphasising practical points and providing up to date information on this rapidly changing subject. Edited by David Mitchell, consultant physician in respiratory medicine, St Mary's Hospital, London, and Ashley Woodcock, consultant chest physician, Wythenshawe Hospital, Manchester, *AIDS and the lung* is an indispensable handbook for respiratory physicians, especially those with limited experience of dealing with AIDS—and for everyone concerned with protective measures in bronchoscopy units and pulmonary function laboratories.

UK £8.95; Abroad £10.00
BMA members £8.45 or £9.50 including postage, by air abroad

Available from: BRITISH MEDICAL JOURNAL, PO BOX 295, LONDON WC1H 9TE, *any leading bookseller or the BMJ bookshop in BMA House.*

Please enclose payment with order, *or* send us full details of your MASTERCARD, VISA *or* AMERICAN EXPRESS credit card.

German?
I can't read German

BUT
there are detailed English abstracts

Der Anaesthesist

Zeitschrift für Anästhesie · Intensivmedizin · Notfall- und Katastrophenmedizin · Schmerztherapie

6/92

- Gasproben in der Säuglingskapnometrie 307
- Hypoxie in der unmittelbar postoperativen Phase 313
- Neue Hydroxyethylstärke-Präparation 318
- Zusatz von Äthylalkohol zur Spülflüssigkeit 324
- Überwachung des Patienten im Aufwachraum 331
- Propofol versus Midazolam 336
- Beatmung neonatologischer Patienten 342
- Entzündliche Fistel nach Periduralkatheter 348
- Der Notruf 348
- Postoperative Schmerztherap… nach Hyperektomien 354
- Kinking der Arteria carotis interna 361
- Leserbriefe 365

Springer-Ve…

ORIGINALIEN

Anaesthesist (1992) 41: 339–347 © Springer-Verlag 1992

Histaminfreisetzung bei der Einleitung von Kombinationsnarkosen mit Nalbuphin oder Fentanyl *

Modulierung der Reaktion durch die Prämedikation Promethazin/Pethidin

W. Dick[1], W. Lorenz[2], D. Heintz[1], H. Sitter[2] und A. Doenicke[3]

[1] Klinik für Anästhesiologie, Johannes Gutenberg-Universität Mainz
[2] Institut für Theoretische Chirurgie, Philipps-Universität Marburg
[3] Institut für Anästhesiologie, Ludwig-Maximilians-Universität München

Zusammenfassung

In einer kontrollierten klinischen Studie an 24 allgemeinchirurgischen Patienten wurde die Histaminkonzentration während der Einleitungsphase einer Kombinationsnarkose mit Nalbuphin (1 mg/kg) oder Fentanyl (5 µg/kg) untersucht. Zur Prämedikation erhielten die Patienten Promethazin (Atosil®) und Pethidin (Dolantin®) 30 min vor den Opioiden. Die Narkoseeinleitung erfolgte mit Alcuronium-Flunitrazepam-Thiopental-Succinylcholin. Nach der Intubation wurde die Analgesie mit Nalbuphin oder Fentanyl aufrechterhalten. Nalbuphin und Fentanyl erwiesen sich als Histaminfreisetzer mit einer mehr als 40%igen Inzidenz. Nalbuphin aber modulierte (potenzierte) noch dazu die Histaminfreisetzung durch die Kombination Alcuronium-Flunitrazepam-Thiopental. Dieser Unterschied zwischen Nalbuphin und Fentanyl war statistisch signifikant (Inzidenz 46% gegen 9%!). Eine direkte Korrelation zwischen Histaminfreisetzung und hämodynamischer Instabilität konnte nicht nachgewiesen werden. Auch eine detaillierte Kausalitätsanalyse mit bedingten Wahrscheinlichkeiten und der Annahme einer beitragenden Determinante für Histamin ergab, daß die Histaminfreisetzung die gemessenen hämodynamischen Parameter kaum beeinträchtigt. Eine mögliche Ursache dieser Ergebnisse besteht in der zeitgerechten vorherigen Gabe von Promethazin, das sowohl eine starke H_1-antagonistische Wirkung wie auch eine H_2-antagonistische Wirkung entfaltet.

Schlüsselwörter

Histamin – Randomisierte Studie – Nalbuphin – Fentanyl – Anästhesierisika

Histamine release during induction of anaesthesia with nalbuphine or fentanyl. Modulation of the reaction by premedication with promethazine/pethidine

Abstract

In a controlled clinical trial in patients admitted for general surgery (mainly abdominal and thyroid) histamine release following nalbuphine 1 mg/kg i.v. versus fentanyl 5 µg/kg i.v. was studied in the course of an otherwise routine induction with promethazine-pethidine as premedication 30 min before the opioids and alcuronium-flunitrazepam-thiopental 5 min later. Succinylcholine was given before intubation and further analgesia was obtained by repeated administration of either nalbuphine or fentanyl. Plasma histamine levels were measured by a specific fluorometric assay, heart rate and blood pressure were measured for assessing hemodynamics, and clinical signs of anaphylactoid reactions such as skin eruptions and arrhythmias were registered.

Results. Nalbuphine and fentanyl both released histamine with an incidence of more than 40%. In addition, nalbuphine potentiated the histamine release evoked by the sequential administration of alcuronium-flunitrazepam-thiopental in one complex of application. The incidence of histamine release in the nalbuphine group was 6/13 = 46%, in the fentanyl group only 1/11 = 9% (chi² test, $P < 0.05$). Furthermore, this study showed high histamine levels after succinylcholine and intubation in a relation to time of administration that suggested histamine release as a stress response to intubation. Finally the incidence of histamine release after a second injection of the opioids was still 30%. A direct correlation between plasma histamine levels, hemodynamic changes, and skin reactions could not be shown. A detailed causality analysis with histamine release as a contributory determinant showed histamine release less detrimental to hemodynamic stability than the opposite, which had been expected. However, the promethazine administered 30 min before induction of anaesthesia had strong H_1- and H_2-receptor antagonistic activity and was given with optimum timing for H_1- and H_2-prophylaxis.

Conclusion. The study demonstrated that histamine release during anaesthesia and surgery depends strongly on the time sequence of drugs and

Edited by:
A. Doenicke (Editor-in-chief)
W. List, H. Schaer

Indexed in Current Contents

Corresponding Editors:
B. R. Brown Jr., Tucson
R. D. Miller, San Francisco
M. F. Roizen, Chicago
A. Spence, Edinburgh

Springer
International

Free copy

I would like to receive a specimen copy of

tm.44/MPPZ/V/1

Der Anaesthesist *Zeitschrift für Anästhesie · Intensivmedizin · Notfall- und Katastrophenmedizin · Schmerztherapie*

Name

Address

Send to: Springer-Verlag, Customer Services, Tiergartenstr. 17, W-6900 Heidelberg, FRG

British Journal of Anaesthesia 1993; 70: 495

BOOK REVIEWS

ABC of Transfusion, 2nd Edn. Edited by M. Contreras. Published (1992) by BMJ Publishing Group, London. Pp. 66; indexed; illustrated. Price £12.95.

The first edition of this paperback was a compilation of 16 articles which appeared in the *British Medical Journal*. After only a 2-year interval a second edition is available. I understand that this is because of the success of the first edition and because of the significant changes in the labelling of blood and blood products which has necessitated the change of all illustrations, in this heavily illustrated work, which feature pack labels. The multi-authorship has acquired an additional name and the format has remained essentially unaltered. Careful comparison of the two editions confirms changes of detail in a majority of chapters to bring the material completely up to date, relating to matters, for example, of pretesting of donations for antibody to hepatitis C virus and HIV 2.

Overall the book is aimed, successfully, at those who use blood but who work in specialties other than transfusion medicine, and this is emphasized by the editor. It contains a great deal of what the trainee anaesthetist, theatre nurse and operating department assistant need to know about blood transfusion from donor to clinical area and much more besides. It should be read by all these groups, as it is admirably succinct (62 pages of text) and perhaps also by some of us who consider ourselves fully trained.

The concluding chapter by the National Director of the Blood Transfusion Service in England and Wales confirms that the U.K. is now self sufficient in blood and blood products—a situation which can only be maintained by intelligent usage, as so carefully set out in the book.

J. K. Wood

British Medical Bulletin: A Series of Expert Reviews. Pain, Mechanisms and Management. Edited by J. C. D. Wells and C. J. Woolf. Published by Churchill Livingstone, Edinburgh. Pp. 791; indexed; illustrated. Price £33.00.

This edition of the quarterly *British Medical Bulletin* is concerned with pain, its mechanisms and management. The editors have assembled a host of well-known clinicians and scientists in order to provide 18 relatively short reviews on nearly every aspect of pain, both acute and chronic. There is no logical format to the book, but the chapters can be divided broadly into those concerned with basic physiology, clinical practice, pharmacology and psychology.

Woolf gives an excellent account of the central generation of acute pain and there are chapters on the chemical activation of nociceptive peripheral neurones, mechanisms of acute visceral pain and peripheral and central mechanisms of neuropathic pain. These purely scientific reviews are probably the best in the book; each chapter is well written, referenced and illustrated.

The clinical reviews are in general very good also, but some suffer from the fact that the authors have been asked to cover very large areas of interest in relatively short articles. Consequently, some of these tend to be rather superficial, but they do provide an excellent start for the reader with little knowledge of the subject. An example of this is the chapter describing the clinical management of acute pain. This is an enormous area and the authors have attempted to be very comprehensive in their treatment of the subject. Consequently, it lacks detail. Other reviews of clinical practice include the management of sympathetic pain, neurogenic pain syndromes and pain in children.

There is a fine review of the clinical pharmacology of opioids in this book and articles concerned with psychological aspects of pain, both genesis and treatment, are well written and balanced.

Who will find this book useful? It is to be recommended for all those sitting the F.R.C.Anaes. Part 3 examination and for those clinicians who are not in the field of pain management but feel that they need a broad picture of present clinical and academic activity in this specialty. It is not for, and I suspect not aimed at, specialists in pain management.

D. Rowbotham

Specialty Medical Audit (Medical Audit Series 4). By C. Shaw. Published by King's Fund Centre, London. Pp. 206; indexed; illustrated. Price £7.50.

It is surprising that such a simple concept as medical audit has created so many different interpretations and methods of application. Every medical specialty has developed audit tailored to its own requirements, so that at the present time medical audit has a myriad of facets which may be difficult to make sense of.

This book gives a snap-shot in time to convey the current state of medical audit in acute hospital services in the U.K. The first half of the book gives a global description of medical audit from its history and national organization to the principles of its practice, common methods of application and the resources required to undertake it. The second half is separated into chapters describing medical audit in each of the major hospital acute specialties.

The section on Anaesthetics and Intensive Care gives a short account of most of the published work on anaesthetic audit and there is a good selection of references. It is disappointing that Intensive Care does not feature very greatly, although this probably reflects the volume that has been written on this subject. Subjects covered include national guidance from the College, a brief description of difficulties encountered in organizing departmental audit and various auditing methods, from topic review to the use of key indicators and adverse patient events. CEPOD is described, and methods of data collection are discussed. Critical incident reporting is barely mentioned, as is the interface with risk management. It is interesting to make comparisons of audit across specialties, and in this context, most specialities involve sampling of notes and cases, which does not seem to feature in anaesthetic audit.

In summary, this small book acts as a good practical manual of audit methods for those involved in hospital audits and gives an overview of the framework that has been created nationally for medical audit.

A. G. H. Cole

Management of Acute Pain: A Practical Guide. Edited by L. B. Ready, W. T. Edwards and the Task Force on Acute Pain. Published by IASP Publications, Seattle. Pp. 73; indexed; illustrated. Price $15.

This handbook is the first product of the International Association for the Study of Pain Task Force on Acute Pain. The Task Force, chaired by Dr L. Brian Ready, is mainly American, with some representation from Europe and Australia. This is a slim book (unfortunately A4 sized) of 70 pages, which aims to provide practical bedside information for those treating patients with acute pain. It is not intended to be a comprehensive stand-alone book on techniques or a review of the growing literature on Acute Pain Management. The views expressed are those of the members of the Task Force and references are limited.

There are six chapters, covering the mechanisms of acute pain, the pharmacology of opioids, local analgesic drugs and NSAID, adult and paediatric postoperative pain and the management of trauma and burns-related pain. Many readers will consider the book because of their interest in adult postoperative pain—unfortunately there are only 2½ pages on this topic.

The strength of this book, however, lies in the overview of the subject, the coverage of areas such as acutely painful medical conditions and acute cancer pain and the abundance of flow diagrams, tables and lists throughout the book. Errors in dosages have crept in, however; for example, the infusion dose of morphine for neonates is given as 10 *mg* kg^{-1} h^{-1}.

This is a very useful publication designed to be used as a companion to the *U.S. Department of Health Clinical Guidelines on Acute Pain Management*. Between them, they offer a very practical guide to the subject. It is a pity that both are not designed to fit in a white coat pocket.

R. G. Wheatley

Papers for publication and all editorial communications
should be addressed to:
Professor G. Smith,
Editor, British Journal of Anaesthesia,
University Department of Anaesthesia,
Leicester Royal Infirmary,
Leicester LE1 5WW.
Telephone: 0533 470141
Fax: 0533 854487

All **business communications** should be sent to the Publishers: Professional & Scientific Publications Ltd, BMA House, Tavistock Square, London WC1H 9JR.

The GUIDE TO CONTRIBUTORS may be found in the advertisement section of this issue (pages ii, iv & vi).
Published monthly. Annual subscriptions: Worldwide £125.00; USA only $198.00 (direct orders only). Trainee rate: Worldwide £69.00. Airmail rates on application. ISSN 0007–0912. Orders must be accompanied by payment; cheques should be made payable to Professional and Scientific Publications. Orders and payments should be sent to Professional and Scientific Publications, BMA House, Tavistock Square, London WC1H 9JR. Orders in the United States of America may be sent to Professional and Scientific Publications, Box 560B, Kennebunkport, Maine 04046.

Group Advertisement Director, Mr R. Hayzen.
Advertisement Manager, Mr A. Allsop.
Publishing Manager, Mr D. Shaw.
BMA House, Tavistock Square, London WC1H 9JR. 071-387 4499.

Whilst every effort is made by the publishers and editorial committee to see that no inaccurate or misleading data, opinions or statement appear in this Journal, they wish to make it clear that the data and opinions appearing in the articles and advertisements herein are the responsibility of the contributor or advertiser concerned. Accordingly, the publishers and the editorial committee and their respective employees, officers and agents accept no liability whatsoever for the consequences of any such inaccurate or misleading data, opinions or statements. Whilst every effort is made to ensure that drug doses and other quantities are presented accurately, readers are advised that new methods and techniques involving drug usage, and described within this Journal, should only be followed in conjunction with the drug manufacturer's own published literature.

© Copyright: 1993 *British Journal of Anaesthesia*
All rights reserved. No part of this publication may be reproduced, stored in a retrieval system, or transmitted in any form by any means, electronic, mechanical, photocopying, recording or otherwise, without the prior permission of the *British Journal of Anaesthesia*, requests for which should be addressed to the **Editor**.

Published by Professional and Scientific Publications.
Printed in Great Britain by the University Press, Cambridge.

"*I would have everie man write what he knowes and no more.*"—MONTAIGNE

BRITISH JOURNAL OF ANAESTHESIA

VOLUME 70, No. 5 MAY 1993

EDITORIAL

DOUBLE-LUMEN TUBES

Double-lumen endobronchial tubes (DLT) were introduced originally by Bjork, Carlens and Freiberg [1] for differential bronchospirometry in awake patients. Nowadays, this technique is rarely used and the DLT has become synonomous with anaesthesia for intrathoracic procedures. Its main use is to enable surgeons to perform operations on the so-called quiet or non-dependent, collapsed lung. Naturally, most of these procedures are lung resections but, increasingly, these tubes are also being used during oesophageal, diaphragmatic, skeletal and closed cardiac procedures [2].

The construction and placement of these tubes was governed originally by bronchial anatomy. Indeed, this anatomy has stimulated considerable research into both accurate placement and its confirmation [3]. Over the years, many of these tubes were placed blindly and confirmation based on the old maxim of "looks good, feels good and sounds good". Recent papers, however [4, 5], have questioned if such a maxim is adequate in modern practice.

The major problem has always been the varying origin of the right upper lobe bronchus. Classically, it arises from the lateral wall of the right main bronchus, about 2.5 cm from the carina, and is about 1.5 cm in diameter. However, its origin may vary considerably and it has even been recorded as arising from the trachea [6]. Clearly, the chances of mal-alignment on the right side are much greater than on the left side, where such abnormalities are rarely seen. Consequently, left-sided tubes are more popular than right-sided. Yet, even left-sided tubes may be placed badly and migrate, particularly when the patient is turned from the supine to the lateral position [7].

What steps can be taken to try and reduce the incidence of mal-alignment? There is no doubt that preoperative rigid or fibreoptic bronchoscopy is the first step to enable the anaesthetist to inspect the bronchial tree, particularly the right side, and to note potential difficulties.

The next action, after blind introduction of the DLT, must be to confirm that the tube is in the correct place. Classically, this is performed using cuff inflation, alternate clamping and auscultation. More recently, direct inspection of the bronchial tree with a fibreoptic bronchoscope has been proposed to ensure correct placement [8]. With a left-sided tube in place, it is relatively easy to pass the bronchoscope and visualize the carina between the left upper and lower lobes. With the right-sided tube, the task is more difficult. Not only does the anaesthetist need to define clearly the bronchus intermedius, but he or she must attempt also to manipulate the tip of the bronchoscope into the right upper lobe bronchus. This challenge is another reason why left-sided tubes are preferred for the majority of intrathoracic procedures. Yet, if the left main bronchus is abnormal or a left-sided tube cannot be passed, the right-sided tube should be used. Therefore, it is advisable that anaesthetists with a large thoracic surgical practice should maintain and teach their skills with right-sided tubes.

A second approach, which is novel and published in this edition of the Journal, is to use both pressure and volume loop spirometry [9]. In essence, the patient acts as his/her own control, with subsequent patterns compared against that control. Any alteration between the former and the latter is taken as evidence of mal-alignment. Using this technique, Bardoczky and colleagues have shown that approximately 40 % of all DLT passed in their practice were mal-aligned after fibreoptic bronchoscopy. Further, approximately 66 % of these could be detected using spirometric loops.

What was also of great concern was that, after the turning and positioning of the patient, a further 33 % of tubes migrated from the "initial correct or corrected position". Such a high incidence could certainly account for inadequate ventilation occasionally seen during one-lung anaesthesia. Bardoczky and colleagues adjusted the position of the tubes by using both fibreoptic bronchoscopy and spirometric loops. Thus the modern anaesthetist has additional apparatus to promote increased patient safety.

One of the other complications of the passage of DLT is trauma to the respiratory passages in general, and bronchial rupture in particular [10, 11]. This used to be thought to be caused by faulty technique causing tearing of the bronchial mucosa and splitting of the bronchus. In order to prevent such damage, malleable tubes constructed of p.v.c., with low pressure–high volume cuffs were introduced into clinical practice. In addition, the right-sided tubes had "angled cuffs" to counteract possible mal-alignment with the right upper lobe bronchus [12]. However, investigations have shown that the traditional method of inflating both the tracheal and bronchial cuffs may produce intercuff pressures in excess of 60 cm Hg [13]. This pressure was not only more than twice that required for an efficient seal, but also considerably greater than the capillary arterial pressure. Such large pressures could cause direct ischaemic mucosal damage and possibly lead to bronchial tearing [14]. It may be, therefore, that cuff inflation pressures must be monitored far more carefully in future.

Modern practice using DLT has improved considerably. The onset of breath-to-breath monitoring of end-tidal carbon dioxide, fibreoptic bronchoscopy and spirometry loops have reduced the incidence of complications. In addition, the constant monitoring of oxygen saturation has enabled the safety of patients presenting for thoracic surgical procedures to be improved dramatically over the past decade.

R. S. Vaughan
Cardiff

REFERENCES

1. Bjorck VO, Carlens E, Freiberg O. Endobronchial anaesthesia. *Journal of Thoracic and Cardiovascular Surgery* 1953; **14**: 60.
2. Vaughan RS. Endobronchial intubation. In: Latto IP, Rosen M, eds. *Difficulties in Tracheal Intubation*. London: Baillière-Tindall, 1985; 156–172.
3. Benumof JL, Partridge BL, Salvatierra C, Keating J. Margin of safety in positioning modern endobronchial tubes. *Anesthesiology* 1987; **67**: 729–738.
4. Hurford WE, Alfille PH, Ballin MT, Behringer E, Cullen DJ, Haspel K, Wilson RS, Zapol WM. Placement and complications of double lumen endobronchial tubes. *Anesthesia and Analgesia* 1992; 74: S141.
5. Brodsky JB, Shulman MS, Mark JBD. Malposition of left sided double lumen endobronchial tubes. *Anesthesiology* 1985; **62**: 667–669.
6. Last RJ. The thorax. In: *Anatomy. Regional and Applied*, Section 4. Edinburgh: Churchill Livingstone, 1984.
7. Saito S, Dohi S, Nailo H. Alteration of double lumen endobronchial tube positions by flexion and extension of the neck. *Anesthesiology* 1985; **62**: 696–697.
8. Ovassapian A. *Fiberoptic-Aided Bronchial Intubation in Fiberoptic Airway Endoscopy in Anesthesia and Critical Care.* Raven Press: New York, 1990.
9. Bardoczky GI, Levarlet M, Engelman E, deFrancquen P. Continuous spirometry for detection of double-lumen endobronchial tube displacement. *British Journal of Anaesthesia* 1993; **70**: 499–502.
10. Wagner DL, Gammaage GW, Wong MI. Tracheal rupture following the insertion of a disposable double lumen endotracheal tube. *Anesthesiology* 1985; **63**: 698–700.
11. Burton NA, Fall SM, Lyons T, Graeber GM. Rupture of the left mainstem bronchus with a polyvinylchloride double lumen tube. *Chest* 1983; **83**: 928–929.
12. Clapham MC, Vaughan RS. Endobronchial intubation. A comparison between polyvinylchloride and red rubber double lumen tubes. *Anesthesia* 1985; **40**: 1111–1114.
13. Cobley M, Kidd JF, Willis BA, Vaughan RS. Endobronchial cuff pressures. *British Journal of Anaesthesia* 1993; **70**: 576–578.
14. Seegobin ED, Van Hasselt G. Endotracheal cuff pressure and tracheal blood flow; endoscopic studies of effects of four large volume cuffs. *British Medical Journal* 1984; **228**: 965–968.

British Journal of Anaesthesia 1993; 70: 499–502

ORIGINAL ARTICLES

CONTINUOUS SPIROMETRY FOR DETECTION OF DOUBLE-LUMEN ENDOBRONCHIAL TUBE DISPLACEMENT

G. I. BARDOCZKY, M. LEVARLET, E. ENGELMAN AND P. DEFRANCQUEN

SUMMARY

Flow–volume and pressure–volume loops were measured with continuous spirometry in 49 patients in whom the trachea was intubated "blindly" with a double-lumen endobronchial tube for thoracic surgery. Nineteen endobronchial tubes were malpositioned by fibreoptic bronchoscopic criteria; 63% of these were suspected because of the configuration of the spirometric loops. During positioning of the patient and during operation, 34.7% of the endobronchial tubes migrated from the initially correct or corrected position. The secondary displacements were identified by abnormal loop configurations and confirmed with fibreoptic bronchoscopy. Continuous spirometric monitoring is helpful in detecting endobronchial tube displacement during intubation and surgery. (Br. J. Anaesth. 1993; **70**: 499–502)

KEY WORDS

Anaesthetic techniques; fibreoptic bronchoscopy, one-lung ventilation. Intubation: endobronchial. Monitoring: spirometry.

The position of double-lumen endobronchial tubes (DLT) which have been inserted blindly frequently requires correction after fibreoptic bronchoscopic examination [1, 2]. The precisely positioned DLT can be displaced when the patient is moved to the lateral position [3] and may be dislodged during intraoperative manipulation of the pulmonary hilum. Malposition or displacement of the DLT, with subsequent impaired gas exchange, is one of the most difficult situations the anaesthetist may encounter during one-lung ventilation. During operation, the position can be corrected with fibreoptic bronchoscopy or the surgeon can replace the tube manually when the chest is opened. Both procedures are time consuming. Estimation of the dependent lung ventilation is possible [4, 5] by watching mediastinal movements and by monitoring inspiratory airway pressure changes, end-tidal concentration of carbon dioxide and pulse oximetry.

The spirometer of the Ultima SV (Datex Instr. Corp. Helsinki, Finland) provides continuous data on adequacy of ventilation and oxygenation. It incorporates inspiratory airway pressure, volume, flow and end-tidal carbon dioxide measurements at the tracheal tube. The in-line respiratory monitor is supplied with flow–volume and pressure–volume loop displays providing information about the compliance and flow characteristics of the ventilatory system [6, 7]. Changes in compliance and the expiratory flow characteristics are continuously and visually illustrated by the changing form of each loop and can be compared with the baseline curves stored in memory. The visual display of the numeric information may be especially helpful during thoracic surgery. Therefore, the present study was designed to investigate the change in configuration of the displayed loops resulting from malposition or migration of the DLT.

PATIENTS AND METHODS

The study was approved by our hospital's Ethics Committee and informed consent was obtained during a 5-month period from 49 consecutive adult patients undergoing elective right or left thoractomy requiring one-lung ventilation.

Three-lead ECG, invasive radial arterial pressure and arterial oxygen saturation were monitored continuously. The respiratory variables were observed with the flow sensor and gas sampling probe of the Ultima.

Anaesthesia was induced and maintained with a variable rate continuous infusion of propofol; pancuronium was used for neuromuscular block. In all patients, the bronchus of the dependent lung was intubated in a "blind" fashion with a double-lumen endobronchial tube of appropriate size (Broncho-Cath, Mallinckrodt Laboratories, Athlone, Ireland). After intubation, the tracheal and bronchial cuffs were inflated with air and the common connector of the DLT was attached to the flow sensor. Pressure–volume and flow–volume loops were recorded with the two lungs ventilated with 10 ml kg^{-1} tidal volume at a rate of 10–12 b.p.m. To keep the volume constant, the ventilator settings were the same throughout the procedure.

The ability to isolate each lung was assessed by alternately clamping the tracheal and bronchial limbs. The apical, anterior and axillary area of each hemithorax were auscultated, and both limbs were examined for leaks. Pressure–volume and flow–volume loops were recorded again, with the tracheal lumen clamped and judgement was made about the position of the DLT based on the configuration of

GIZELLA I. BARDOCZKY, M.D.; MICHELINE LEVARLET, M.D.; EDGARD ENGELMAN, M.D.; PHILIPPE DEFRANCQUEN, M.D.; Department of Anaesthesiology and Thoracic Surgery, Erasme University Hospital, Free University of Brussels, 808 Route de Lennik, 1070 Brussels, Belgium. Accepted for Publication: October 12, 1992.

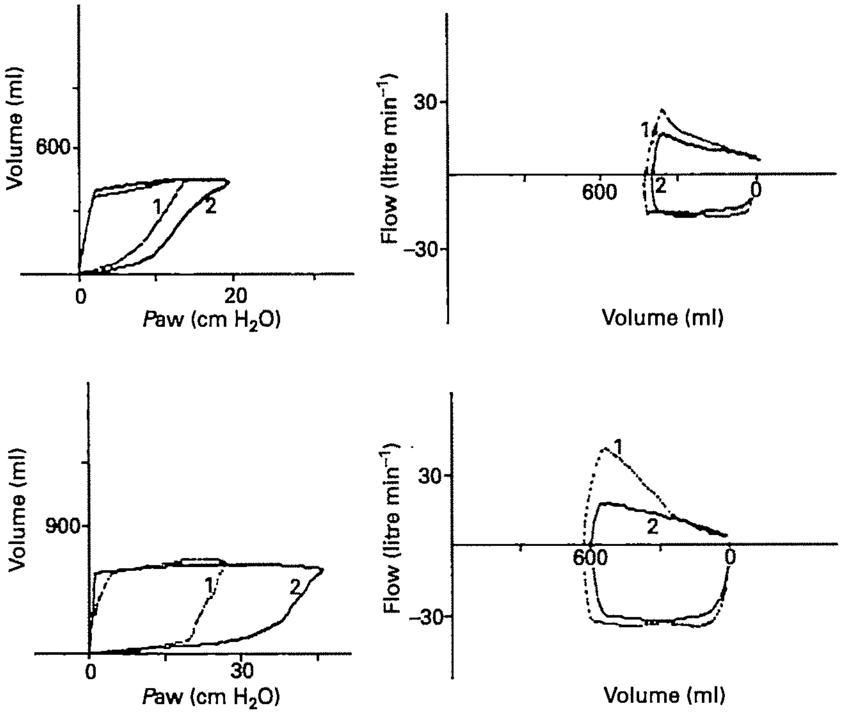


FIG. 1. Pressure–volume loops (left panel) and flow–volume loops (right panel) recorded during two-lung ventilation (1) and during one-lung ventilation (2). Upper traces: double-lumen tube placed correctly. Lower traces: double-lumen tube malpositioned.

the loops. Fibreoptic bronchoscopy was then performed to determine if the bronchoscopic findings confirmed the impressions based on the flow– and pressure–volume loops. When the position was not adequate according to the criteria described by Smith, Hirsch and Ehrenwerth [1], it was corrected under direct bronchoscopic examination.

After the patient was placed in the lateral position, the tracheal lumen of the DLT was clamped, flow–volume and pressure–volume loops were recorded and interpreted. Fibreoptic bronchoscopy was repeated and correction of the DLT position was made when required.

During operation and during the period of one-lung ventilation, the flow–volume and pressure–volume loops were monitored continuously. When alteration of the configuration of the curve was noted, recordings were made and fibreoptic bronchoscopy performed. When secondary migration was seen by fibreoptic bronchoscopy, the position of the DLT was corrected.

RESULTS

The mean age of the patients was 57.3 yr (range 14–74 yr), mean height 167 cm (range 151–183 cm) and mean weight was 66.8 kg (range 38–103 kg). In the 49 patients studied; 19 right-sided and 30 left-sided DLT were positioned; 19 (38.7 %) proved to be placed inaccurately during blind intubation (table I). Based on the flow–volume/pressure–volume loop configurations alone, 12 DLT were judged not to be in the satisfactory position after intubation (confirmed by fibreoptic bronchoscopy), and seven other malpositions were recognized by fibreoptic bronchoscopy. From all of the initially correct, or corrected positions, 17 DLT (34.7 %) migrated subsequently: five (10.2 % of all cases) during change to the lateral position and 12 (24.5 %) during surgical manipulation. Sixteen of the 17 secondary displacements were identified by the aberrant pressure–volume and flow–volume curves.

TABLE I. *Position-related problems diagnosed with flow–volume (FV) and pressure–volume (PV) loops and confirmed with fibreoptic bronchoscopy (FOB) in 49 patients in whom the trachea was intubated with a double-lumen endobronchial tube. (Number of right sided double-lumen endobronchial tubes in parentheses)*

Type of malposition	FV/PV loops	FOB
Initial malposition	12 (4)	19 (6)
Postural displacement	5 (2)	5 (2)
Intraoperative migration	11 (3)	12 (4)
Total malpositions	28 (9)	36 (12)

The configuration of the pressure–volume PV loop did not change significantly during one-lung ventilation compared with two-lung ventilation when the DLT was positioned correctly. Only the slope of the curve shifted slightly to the right (fig. 1). When the DLT was placed incorrectly, the form of the pressure–volume curve altered, the inspiratory and expiratory limb becoming distorted and the area of the curve enlarged abnormally (fig. 1).

Of the initially malpositioned DLT, seven were advanced too far, six were not advanced sufficiently and two left-sided tubes were twisted to the right. From the six initially malpositioned right-sided DLT, obstruction of the right upper lobe orifice was noted with fibreoptic bronchoscopy in five instances.

Only one patient exhibited $Sp_{O_2} < 90\,\%$ during one-lung ventilation. Eleven patients had airway pressures > 40 cm H_2O and, on nine occasions,

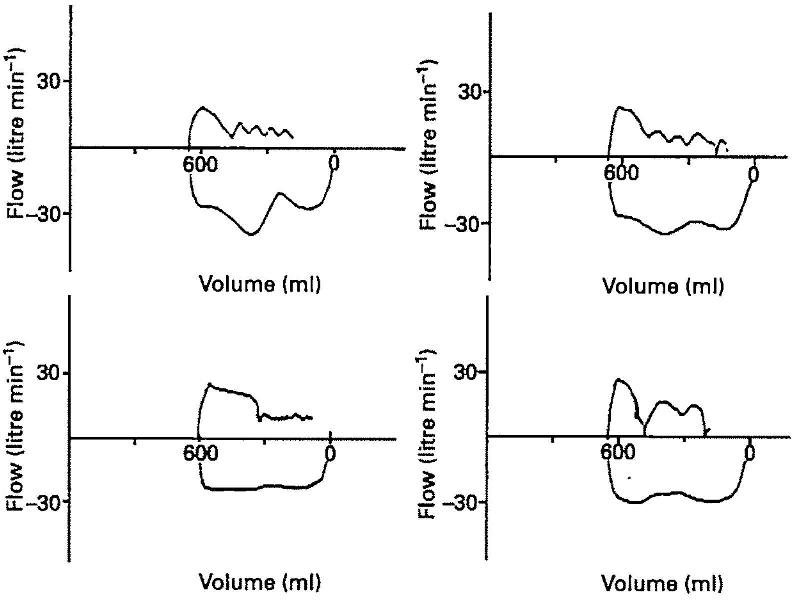


FIG. 2. Flow–volume loops distorted by surgical manipulation.

intrinsic PEEP up to $+9+11$ cm H_2O or persistent expiratory flow was noted on the flow–volume loops during one-lung ventilation.

DISCUSSION

Of the 49 DLT, 19 (38.7 %) were malpositioned and then repositioned with fibreoptic bronchoscopy during initial placement. Of the 19 initial malpositions, 12 (63 %) were suspected because of the configuration of the pressure– and flow–volume loops. The smaller proportion of loop-recognized initial malpositions is likely to be the result of individual variations in the characteristics of the pressure–volume and flow–volume loops in a population with altered lung function. For this reason, a baseline curve has to be established for each patient in the dorsal position during two-lung ventilation. This curve can be stored in the memory of the monitor and compared with those obtained after positioning of the patient and during surgery.

We have not found data in the literature concerning the incidence of secondary displacements. In our study, with continuous spirometric evaluation, 92 % of secondary migrations were identified because of the altered configuration of pressure– and flow–volume curves and confirmed subsequently by fibreoptic bronchoscopy.

The pattern of the flow–volume loop is determined by the mechanical properties of the total respiratory system (the lung and thorax of the patient, the endobronchial tube and the ventilator), but it is reproducible for that given patient. The curve is not very different during two- or one-lung ventilation when the DLT is positioned accurately (fig. 1).

Malposition of a DLT can result in expiratory flow limitation, increased inspiratory or expiratory resistance, or both, because of lumen obstruction and delayed deflation or incomplete emptying of the lung. This results in "cut-off" of the high flow rates and a flat, horizontal expiratory limb (fig. 1). Surgical manipulation around the lung hilum during dissection also changes the pattern of the flow–volume loops, especially the expiratory limb. It becomes ragged or serrated and the expiratory limb may reach the volume axis at a volume greater than zero (fig. 2). Depending on the degree of obstruction caused by the malposition of the endobronchial tube, or by the surgical manipulation of the non-dependent lung, the configuration of the flow–volume loop may be distorted or even grotesque. These loops may illustrate visually the phenomenon of persistent expiratory flow described by Larsson, Malmkvist and Werner [8] (fig. 3). In nine patients, we demonstrated increased end-expiratory pressures during one-lung ventilation, occasionally without increased inspiratory airway pressure. With continuous spirometric monitoring of flow– and pressure–volume loops, large numbers of initial and intraoperative DLT displacements were detected by the altered configuration of either the pressure–volume or the flow–volume loop. As the change of DLT position can be seen immediately from the displayed curves, appropriate action can be initiated, and the harmful effects of increased airway pressure, hyperinflation, hypoventilation and hypoxaemia can be avoided.

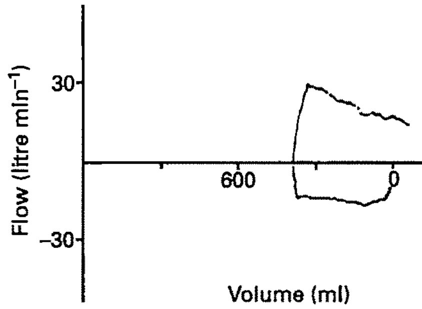


FIG. 3. Flow–volume loop with persistent expiratory flow.

In conclusion, continuous spirometry is a promising method of monitoring ventilation during anaesthesia for lung surgery. The margin of safety of the correct position for the DLT is narrow:

movement of the patient and manipulation can easily displace or dislodge the tube from the correct position. Comparison of the displayed loops with those recorded and considered normal for individual patients is highly desirable, as the curves are slightly different in each patient. Small deviations from baseline can signify a position-related problem, but the exact site and nature of obstruction cannot be diagnosed and corrected based on the altered loop configuration alone. Fibreoptic bronchoscopy is necessary to correct the problem.

REFERENCES

1. Smith GB, Hirsch NP, Ehrenwerth J. Placement of double lumen endobronchial tubes. *British Journal of Anaesthesia* 1986; **58**: 1317–1320.
2. Hurford WE, Alfille PH, Ballin MT, Behringer E, Cullen DJ, Haspel K, Wilson RS, Zapol WM. Placement and complications of double-lumen endotracheal tubes. *Anesthesia and Analgesia* 1992; 74: S141.
3. Saito S, Dohi S, Naito H. Alteration of double lumen endobronchial tube position by flexion and extension of the neck. *Anesthesiology* 1985; **62**: 696–697.
4. Brodsky JB, Shulman MS, Mark JBD. Malposition of left-sided double lumen endobronchial tubes. *Anesthesiology* 1985; **62**: 667–669.
5. Benumof JL, Partridge BL, Salvatierra C, Keating J. Margin of safety in positioning modern double-lumen endotracheal tubes. *Anesthesiology* 1987; **67**: 729–738.
6. Bardoczky G, d'Hollander A. Continuous monitoring of the flow–volume loops and compliance during anaesthesia. *Journal of Clinical Monitoring* 1992; **8**: 251–252.
7. Simon BA, Hurford WE, Alfille PH, Haspel K, Behringer EC. An aid in the diagnosis of malpositioned double-lumen tubes. *Anesthesiology* 1992; **76**: 862–863.
8. Larsson A, Malmkvist G, Werner O. Variations in lung volume and compliance during pulmonary surgery. *British Journal of Anesthesia* 1987; **59**: 585–591.

British Journal of Anaesthesia 1993; **70**: 503–507

PATIENT-CONTROLLED EXTRADURAL ANALGESIA TO COMPARE BUPIVACAINE, FENTANYL AND BUPIVACAINE WITH FENTANYL IN THE TREATMENT OF POSTOPERATIVE PAIN

D. W. COOPER AND G. TURNER

SUMMARY

We have assessed the effect of combining extradural bupivacaine and fentanyl in 60 orthopaedic patients who received 0.125% bupivacaine (bupivacaine group), fentanyl 5 µg ml^{-1} (fentanyl group), or 0.125% bupivacaine combined with fentanyl 5 µg ml^{-1} (combined group), delivered by patient-controlled extradural analgesia for 24 h via a lumbar extradural catheter. Adding bupivacaine to fentanyl reduced mean (SD) fentanyl administration from 117 (46) ml to 89 (42) ml ($P < 0.005$). Adding fentanyl to bupivacaine reduced mean bupivacaine administration from 113 (46) ml to 89 (42) ml ($P < 0.05$). There was no significant difference between the groups in pain, nausea, motor block, pruritus or sedation. No patient had a ventilatory frequency less than 10 b.p.m. Hypotension (systolic AP < 100 mm Hg) occurred in two of 20 patients in the fentanyl group, compared with eight of 19 in the bupivacaine group and 10 of 21 in the combined group. The mean total volume of extradural solution administered was greater after knee replacement (126 (46) ml) than after hip replacement (84 (35) ml) ($P < 0.001$). The mean pain score was greater also for knee replacement (16 (10) mm) than for hip replacement (10 (9) mm) ($P < 0.05$). We conclude that extradural bupivacaine and fentanyl were additive in their analgesic actions, resulting in decreased requirements of each individual agent. Knee replacement was found also to be more painful than hip replacement after operation. (Br. J. Anaesth. 1993; **70**: 503–507)

KEY WORDS

Anaesthetic techniques: extradural. Anaesthetics, local: bupivacaine. Analgesia: patient controlled extradural analgesic. Analgesics: fentanyl. Pain: postoperative.

Extradural analgesia using bupivacaine or opioids, alone or in combination, has become a well established and effective means of controlling postoperative pain. To date, much of the work investigating the combination of bupivacaine and opioids relates to patients in labour. These studies demonstrate that the addition of lipid-soluble opioids to bupivacaine results in improved analgesia [1] and can reduce bupivacaine-related side effects [2]. Whilst the use of the combination of bupivacaine and the lipid-soluble opioid fentanyl is gaining in popularity after surgery, it has been investigated less thoroughly than in obstetric practice. Indeed, recent work has produced conflicting results [3–5].

The aim of this study was to use patient-controlled extradural analgesia (PCEA) to compare extradural bupivacaine, fentanyl and the combination of both, for postoperative pain relief. The concentrations of bupivacaine and fentanyl chosen were those used routinely in combination in our centre for postoperative pain relief by extradural infusion. The use of patient-controlled analgesia (PCA) allows patients to titrate analgesics to their own individual requirements and it has been recommended for use in comparative analgesic studies [6].

PATIENTS AND METHODS

After obtaining Hospital Ethics Committee approval and informed consent, we studied ASA I–III patients undergoing knee or hip replacement surgery, and having an extradural inserted as part of their anaesthetic technique.

Patients were educated in the use of PCEA and the 100-mm visual analogue score before operation. All patients were given a combined extradural and general anaesthetic. Premedication, if required, comprised oral temazepam 1–2 h before operation. A Portex extradural catheter was inserted in a lumbar space before, or shortly after, induction of anaesthesia and an extradural block was established with 0.5% bupivacaine 10–15 ml. The L2–3 or L3–4 space was chosen preferentially, otherwise L1–2 or L4–5 was used according to ease of catheter insertion. After an i.v. induction, anaesthesia was maintained with nitrous oxide and a volatile agent in oxygen. Additional intraoperative analgesia, if required, was provided by fentanyl up to 200 µg i.v.

DAVID W. COOPER*, M.B., B.S., F.R.C.ANAES.; GRANT TURNER, M.B., B.S., F.R.C.ANAES., F.A.N.Z.C.A.; Department of Anaesthesia, Royal Perth Hospital, Perth, West Australia. Accepted for Publication: November 11, 1992.

*Present address, for correspondence: Department of Anaesthetics, Freeman Hospital, Freeman Road, Newcastle upon Tyne.

TABLE I. *Details of patients in bupivacaine, fentanyl and combined groups (number (range or SD))*

	Bupivacaine group ($n = 19$)	Fentanyl group ($n = 20$)	Combined group ($n = 21$)
Sex (M/F)	8/11	7/13	8/13
Age (yr)	70 (53–85)	68 (40–82)	71 (50–85)
Weight (kg)	71 (13)	72 (11)	76 (14)
Surgery			
Hip	10	10	11
Knee	9	10	10
Level of extradural			
L1–2	2	0	1
L2–3	2	11	9
L3–4	14	8	9
L4–5	1	0	2
Not recorded	0	1	0

TABLE II. *Details of patients having knee or hip replacement (number (range or SD))*

	Knee replacement ($n = 29$)	Hip replacement ($n = 31$)
Sex (M/F)	9/20	14/17
Age (yr)	70 (50–84)	70 (40–85)
Weight (kg)	73 (12)	73 (13)
Level of extradural		
L1–2	0	3
L2–3	9	13
L3–4	18	13
L4–5	2	1
Not recorded	0	1
Extradural solution		
Bupivacaine	9	10
Fentanyl	10	10
Combined	10	11

At the completion of surgery, the extradural catheter was connected to a Graseby PCA machine which was loaded with a preformulated, randomized syringe of extradural trial solution. This contained 0.125% bupivacaine (bupivacaine group), fentanyl 5 $\mu g\ ml^{-1}$ (fentanyl group), or 0.125% bupivacaine combined with fentanyl 5 $\mu g\ ml^{-1}$ (combined group). The PCA settings allowed for a bolus of 4 ml to be given over 5 min with a lock-out time of 10 min. All patients, anaesthetists and nursing staff were blinded to the patient groupings: the syringes were prepared by one of the authors not involved with patient management.

The study lasted for 24 h from the end of the operation, during which time the patients were managed in a High Dependency Unit. Patients were free to use PCEA from the end of the operation. If analgesia was inadequate, as judged by the patient, nursing or medical staff, a maximum of two 10-ml boluses of trial solution, at least 20 min apart, could be given. If analgesia remained inadequate, the study stopped at that point and the correct catheter position was tested with 10 ml of 1% lignocaine. Data were included if motor and sensory block were elicited.

The volume of PCEA solution administered, including bolus doses, was recorded at 4, 8, 12, 16, 20 and 24 h after operation. Visual analogue score (VAS) was recorded on a 100-mm scale (0 mm = no

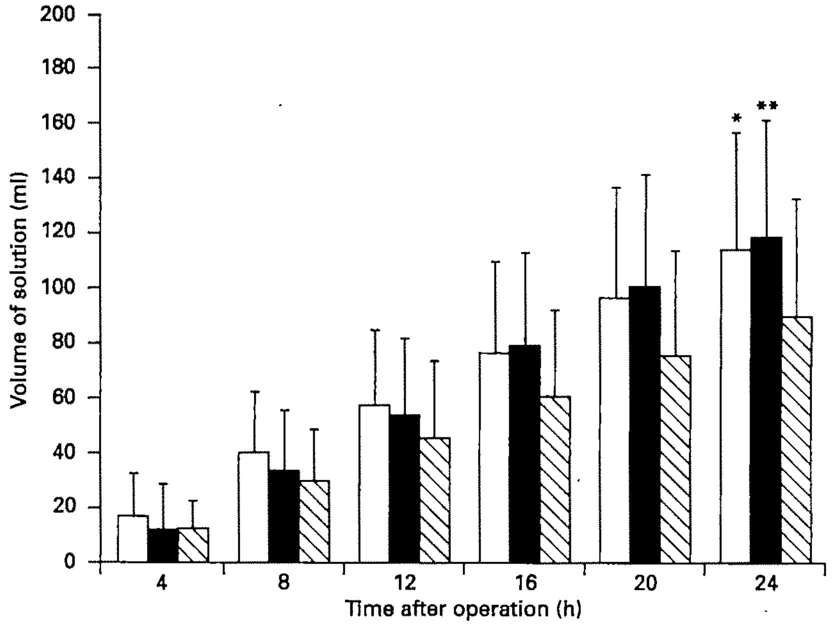


FIG. 1. Mean (SD) cumulative volumes of extradural solution administered for the bupivacaine (□), fentanyl (■) and combined (▨) groups. $^*P < 0.05$; $^{**}P < 0.01$ compared with combined group (Mann–Whitney).

TABLE III. *Mean* (SD) *total volumes of extradural solution used and mean pain scores over 24 h after operation*

	Bupivacaine group	Fentanyl group	Combined group	All groups
Total volume (ml)				
Knee	137 (37) ($n = 9$)	131 (52) ($n = 10$)	112 (46) ($n = 10$)	126 (46) ($n = 29$)
Hip	86 (43) ($n = 10$)	102 (34) ($n = 10$)	68 (23) ($n = 11$)	84 (35) ($n = 31$)
Knee and hip	113 (46) ($n = 19$)	117 (46) ($n = 20$)	89 (42) ($n = 21$)	105 (46) ($n = 60$)
Pain scores (mm)				
Knee	19 (11) ($n = 9$)	14 (6) ($n = 10$)	16 (12) ($n = 10$)	16 (10) ($n = 29$)
Hip	13 (12) ($n = 10$)	11 (8) ($n = 10$)	6 (6) ($n = 11$)	10 (9) ($n = 31$)
Knee and hip	17 (12) ($n = 19$)	12 (7) ($n = 20$)	11 (10) ($n = 21$)	13 (10) ($n = 60$)

pain; 100 mm = worst pain imaginable) at 2, 6, 12 and 24 h after operation. Assessments of nausea, motor block, pruritus and sedation were recorded at the same times on 3-, 5-, 4- and 4-point scales, respectively. Arterial pressure and ventilatory frequency were recorded hourly and more frequently if there was hypotension (systolic AP < 100 mm Hg) or respiratory depression (ventilatory frequency < 10 b.p.m.).

Results were compared using Kruskal–Wallis and Mann–Whitney tests with $P < 0.05$ taken as significant.

RESULTS

We studied 60 patients (tables I and II). The three groups were matched evenly in gender, age, weight and type of operation. Relatively more extradurals were sited at L3–4 than L2–3 in the bupivacaine group compared with the fentanyl and combined groups. Patients having knee or hip replacement surgery were matched evenly within age, weight and type of extradural solution. The ratio of females to males was greater and there were relatively more extradurals sited at L3–4 for knee replacement than for hip replacement patients. A tourniquet was used for all knee replacement surgery.

The mean (SD) total volume of extradural solution administered over the 24-h study period was significantly smaller in the combined group (89 (42) ml), compared with the bupivacaine group (113 (46) ml) and the fentanyl group (117 (46) ml) ($P < 0.05$ and $P < 0.01$, respectively) (fig. 1, table III). Supplementary bolus doses were given to four patients in the bupivacaine group (mean volume 14 ml), three in the fentanyl group (mean volume 17 ml) and three in the combined group (mean volume 15 ml). The mean total volume of extradural solution administered was significantly greater for patients having knee replacement (126 (46) ml) than for those having hip replacement (84 (35) ml) ($P < 0.001$). Supplementary bolus doses were given to seven knee replacement patients (mean volume 16 ml) and three hip replacement patients (mean volume 13 ml).

The mean pain scores over the 24-h study period for the fentanyl group (12 (7) mm) and the combined group (11 (10) mm) were smaller than for the bupivacaine group (17 (12) mm), although this was not significant (fig. 2, table III). The mean pain score was significantly greater for knee replacement patients (16 (10 mm) than for those having hip replacement (10 (9) mm) ($P < 0.05$).

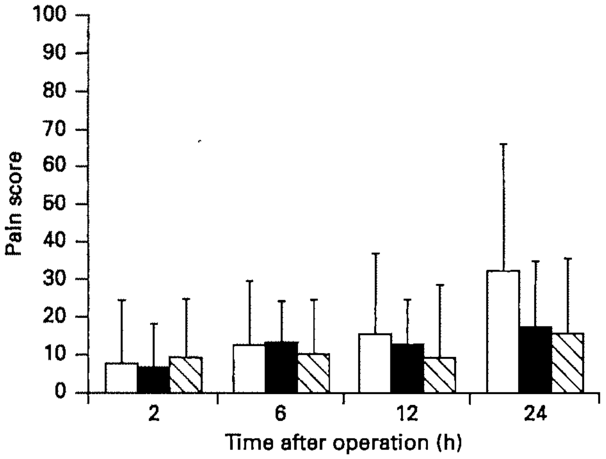


FIG. 2. Mean (SD) pain scores (VAS) for the bupivacaine (□), fentanyl (■) and combined (▨) groups.

TABLE IV. *Percentage of patients in the three groups having nausea, motor block (inability to lift non-operated knee off bed) or pruritus, 2, 6, 12, or 24 h after operation*

	Bupivacaine group	Fentanyl group	Combined group
Nausea (%)	42	40	24
Motor block (%)	53	55	29
Pruritus (%)	16	30	38

Patient gender or positioning of the extradural catheter at L2–3 or L3–4 did not make a significant difference to the volume of solution administered, or pain scores, over the 24-h study period.

Nausea, motor block, pruritus and sedation were not significantly different between the three groups. However, the combined group had less nausea and motor block compared with the two other groups, while the bupivacaine group had less pruritus compared with the fentanyl and combined groups (table IV).

Hypotension (defined as a systolic AP $<$ 100 mm Hg) occurred in four of 19 patients in the bupivacaine group, compared with four of 20 in the fentanyl group and eight of 21 in the combined group after surgery, but before commencement of PCEA. This compared with eight of 19 in the bupivacaine group, two of 20 in the fentanyl group and 10 of 21 in the combined group after commencement of PCEA.

A ventilatory frequency less than 10 b.p.m. was not recorded for any patient after commencement of PCEA. There was no difference in the mean minimum ventilatory frequency between the bupivacaine group (12.8 (1.6) b.p.m.), the fentanyl group (12.5 (2.0) b.p.m.) and the combined group (12.7 (2.1) b.p.m.).

Two patients receiving bupivacaine did not complete the full 24-h study period. One had inadequate analgesia (despite good catheter position) and another found the "numbness" disconcerting and requested withdrawal. A third patient receiving fentanyl requested withdrawal within 2 h because of pruritus. The extradural catheter level was not recorded for this patient.

DISCUSSION

Our results demonstrated that combining extradural bupivacaine and fentanyl decreased requirements of each individual agent. Addition of bupivacaine to fentanyl led to a 24% reduction in fentanyl administration by PCEA, whilst adding fentanyl to bupivacaine led to a 21% reduction in bupivacaine administration by PCEA. This implied that bupivacaine and fentanyl were at least additive in their analgesic actions, and that the contribution of each agent to the combination of both was of a similar magnitude.

These findings differ from those of a similar study [5] using continuous lumbar extradural infusions which found that low-dose bupivacaine did not improve postoperative extradural fentanyl analgesia in orthopaedic patients. That study compared fentanyl 10 $\mu g\ ml^{-1}$ alone and 0.1% bupivacaine combined with fentanyl 10 $\mu g\ ml^{-1}$, given by extradural infusion after knee replacement. The mean doses of bupivacaine and fentanyl administered in the combined group were of the order of 8 $mg\ h^{-1}$ and 80 $\mu g\ h^{-1}$, respectively (ratio of bupivacaine:fentanyl = 1 mg:10 μg). This compared with mean doses of bupivacaine 5.8 $mg\ h^{-1}$ and fentanyl 23 $\mu g\ h^{-1}$ for the knee replacement patients in our combined group (ratio of bupivacaine:fentanyl = 1 mg:4 μg). We suggest that the relatively large dose of fentanyl used in that study may have masked any beneficial effect of the addition of bupivacaine to fentanyl.

More recent work [3], comparing continuous thoracic extradural infusions of 0.2% bupivacaine, fentanyl 10 $\mu g\ ml^{-1}$ and a combination of both, after abdominal aortic surgery, is in greater concordance with our results. In that study, the combined group had superior analgesia compared with each agent used alone. A mean dose of bupivacaine 9.3 $mg\ h^{-1}$ and fentanyl 46 $\mu g\ h^{-1}$ was administered. Whilst the concentrations and doses of bupivacaine and fentanyl used were greater, the dose ratio of the two (1 mg:5 μg) was similar to that used in our study (1 mg:4 μg). The optimum dose ratio for extradural bupivacaine and fentanyl is likely to be closer to these values than that used in the orthopaedic study of Badner and colleagues [5].

The side effects encountered in our study were of a minor nature. There was no significant difference between the groups for nausea, motor block, pruritus or sedation. Respiratory depression (ventilatory frequency < 10 b.p.m.) was not encountered in any group. A systolic AP of < 100 mm Hg was recorded in 20 of 60 patients after commencement of PCEA. In the study comparing similar groups after aortic surgery [3], no patient had a systolic AP of less than 100 mm Hg. It is possible that the administration of small boluses of bupivacaine (5 mg) by PCEA in our study, as opposed to a continuous infusion, contributed to this difference. A more likely explanation is that the invasive monitoring used in the aortic patients enabled more rapid detection and treatment of hypovolaemia, thus preventing hypotension. The problem of postoperative hypotension should be balanced against the reduction in extradural fentanyl requirements and possible reduction in deep vein thrombosis [7] produced by extradural bupivacaine.

A coincidental finding in our study was that, after knee replacement, 50% more extradural solution was used than after hip replacement. Despite this, the average pain score was significantly greater than after hip replacement. We conclude that knee replacement was more painful than hip replacement.

The technique of PCEA was accepted well by this rather elderly group of patients. It allowed patients to administer analgesia more closely to their widely varying individual needs. However, all groups did not quite achieve uniformly low pain scores, in particular the bupivacaine group at 24 h after operation had a greater mean pain score than the two other groups (fig. 2). This may have resulted from regression and tachyphylaxis [8, 9] but, if so, we cannot explain why the patients did not increase the bupivacaine administration to counter this.

There may be advantages in using PCEA routinely. The average hourly amount of bupivacaine or fentanyl used after knee replacement by patients with PCEA in our study was of the order of 33% of that reported for patients with continuous extradural infusions after knee replacement [5, 10]. This is in agreement with a study comparing administration of fentanyl by either PCEA or continuous extradural infusion following abdominal surgery [11]. It was suggested that psychological or pharmacological mechanisms may be responsible for this difference. Reduction in anxiety may have increased the placebo effect of PCEA. Intermittent bolus administration of drugs may have allowed greater CSF penetration of fentanyl than a continuous infusion. In addition, spread of extradural solution after bolus administration may be greater than with infusion. This is more likely to be a factor for fentanyl than for bupivacaine. In order to block knee or hip pain, the spinal analgesic action of fentanyl would occur in the lower thoracic region, as opposed to the lumbar region for bupivacaine. Whatever the mechanism, the potential for PCEA to reduce analgesic dosage, whilst at the same time maintaining analgesic efficacy, warrants further investigation.

ACKNOWLEDGEMENTS

We thank Astra Pharmaceutical for supplying all the extradural solutions and Graseby for loaning us the PCEA pumps.

REFERENCES

1. Reynolds F. Extradural opioids in labour. *British Journal of Anaesthesia* 1989; **63**: 251–253.
2. Phillips G. Continuous infusion epidural analgesia in labor: The effect of adding sufentanil to 0.125% bupivacaine. *Anesthesia and Analgesia* 1988; **67**: 462–465.
3. George KA, Chisakuta AM, Gamble JAS, Browne GA. Thoracic epidural infusion for postoperative pain relief following abdominal aortic surgery: bupivacaine, fentanyl or a mixture of both? *Anaesthesia* 1992; **47**: 388–394.
4. George KA, Wright PMC, Chisakuta A. Continuous thoracic epidural fentanyl for post-thoracotomy pain relief: with or without bupivacaine? *Anaesthesia* 1991; **46**: 732–736.
5. Badner NH, Reimer EJ, Komar WE, Moote CA. Low-dose bupivacaine does not improve postoperative epidural fentanyl analgesia in orthopedic patients. *Anesthesia and Analgesia* 1991; **72**: 337–341.
6. White PF. Use of patient-controlled analgesia for management of acute pain. *Journal of the American Medical Association* 1988; **259**: 243–247.
7. McKenzie PJ. Deep vein thrombosis and anaesthesia. *British Journal of Anaesthesia* 1991; **66**: 4–7.
8. Bromage PR, Pettigrew RT, Crowell DE. Tachyphylaxis in epidural analgesia. I. Augmentation and decay of local anaesthesia. *Journal of Clinical Pharmacology* 1969; **9**: 30–38.
9. Mogenson T, Hjørtso N-C, Bigler D, Lund C, Kehlet H. Unpredictability of regression of analgesia during continuous postoperative extradural infusion of bupivacaine. *British Journal of Anaesthesia* 1988; **60**: 515–519.
10. Prithvi Raj P, Knarr DC, Vigdorth E, Denson DD, Pither CE, Hartrick CT, Hopson CN, Edstrom HH. Comparison of continuous epidural infusion of a local anesthetic and administration of systemic narcotics in the management of pain after total knee replacement surgery. *Anesthesia and Analgesia* 1987; **66**: 401–406.
11. Boudreault D, Brasseur L, Samii K, Lemoing J-P. Comparison of continuous epidural bupivacaine infusion plus either continuous epidural infusion or patient-controlled epidural injection of fentanyl for postoperative analgesia. *Anesthesia and Analgesia* 1991; **73**: 132–137.

British Journal of Anaesthesia 1993; **70**: 508–510

EFFICACY OF CONTINUOUS INTERCOSTAL BUPIVACAINE FOR PAIN RELIEF AFTER THORACOTOMY

C. M. DRYDEN, I. McMENEMIN AND D. J. R. DUTHIE

SUMMARY

*We studied 20 patients undergoing thoracotomy, in a double-blind, placebo-controlled crossover trial of intercostal bupivacaine. Bupivacaine 0.25% was infused at 5 ml h^{-1} through each of two catheters placed in the intercostal space at operation. Mean (95% confidence limits) 24-h requirements for morphine from a patient-controlled analgesia device were 29 (22–37) mg during bupivacaine infusion and 44 (32–57) mg during saline infusion (*P = *0.04). Patients also recorded significantly smaller visual analogue scores for pain during bupivacaine infusion. There were no adverse effects related to the intercostal infusion of bupivacaine. We conclude that bupivacaine, infused through catheters placed during thoracotomy in the adjacent intercostal spaces, is a useful adjunct to systemic opioid analgesia* (Br. J. Anaesth. 1993; **70**: 508–510)

KEY WORDS

Anaesthetic techniques, regional: intercostal block. Pain: postoperative.

Lateral thoracotomy wounds are amongst the most painful [1], but local anaesthetic in the intercostal space has been shown to relieve pain after thoracotomy effectively [2]. Problems associated with percutaneous intercostal nerve block include intravascular injection, puncture of the parietal pleura and a significant failure rate [3, 4]. The risks are increased if repeated injections are used, rather than a catheter technique. Bupivacaine delivered via catheters placed in the intercostal space during surgery has been described recently as a means of providing analgesia after thoracotomy [5]. Our study was designed to assess the analgesic efficacy after thoracotomy of continuous intercostal nerve block compared with placebo.

PATIENTS AND METHODS

After obtaining local Ethics Committee approval and informed written consent, we studied patients admitted for elective surgery through a single lateral thoracotomy incision. Patients were instructed how to use a patient-controlled analgesia device (Graseby 2000, Graseby Medical Ltd, Watford, U.K.). Anaesthetic technique was standardized. Benzodiazepine premedication was provided and anaesthesia was induced with etomidate 0.3 mg kg^{-1}. Anaesthesia was maintained with 0.5–1.5% enflurane and 50% nitrous oxide in oxygen, supplemented with morphine 10 mg i.v. Vecuronium 0.1 mg kg^{-1} i.v. with further increments of 0.03 mg kg^{-1} as required was used to facilitate mechanical ventilation of the lungs. Neuromuscular block was antagonized subsequently with neostigmine 2.5 mg and glycopyrronium 0.5 mg i.v. Immediately before closure of the chest, two 16-gauge extradural catheters (Portex Ltd, Hythe, U.K.) were placed under direct vision, in the intercostal spaces immediately above and below the wound, by feeding the catheters posteriorly from the wound edges, superficial to the parietal pleura, and bringing the catheters out through the chest wall using the Tuohy needles.

Patients were allocated randomly to group A or group B using sealed envelopes. The trial was designed as a crossover study with patients receiving either 0.25% bupivacaine for the first 24 h and saline for the second (group A), or saline for the first 24 h, followed by bupivacaine (group B). The solutions were infused continuously at a rate of 5 ml h^{-1} through each of the two intercostal catheters. Each catheter was primed with 10 ml of the appropriate solution. Both patient and investigator were blind to the nature of the solution.

On regaining consciousness, patients were given further increments of morphine 1–2 mg i.v. until they were comfortable and able to operate the patient controlled analgesia device (PCA). The PCA device was programmed to deliver morphine 1 mg i.v., with a lock-out duration of 3 min.

Morphine consumption from the PCA was recorded hourly throughout the 48 h of the study period. The patients performed visual analogue scores (VAS) of pain on a 100-mm horizontal line at 1, 3, 6, 24 and 48 h after operation. At 4-h intervals, nursing staff graded and recorded the level of pain, sedation and nausea using the scoring systems detailed in table I.

Lopamidol 10 ml (Niopam 300) was injected through the intercostal catheters, before routine

---

C. M. DRYDEN, F.R.C.ANAES.; I. McMENEMIN, F.R.C.ANAES.; D. J. R. DUTHIE*, M.D., F.R.C.ANAES.; Department of Anaesthetics, Western Infirmary, Dumbarton Road, Glasgow G11 6NT. Accepted for Publication: November 30, 1992.

*Present address: Department of Anaesthetics, Papworth Hospital, Papworth Everard, Cambridge CB3 8RE.

Correspondence to C.M.D.

TABLE I. *Scoring systems used by nursing staff to assess pain, sedation and nausea*

Pain	Sedation	Nausea
0 Asleep	1 Fully awake	0 Nil
1 Awake+no pain	2 Slightly drowsy	1 Nausea
2 Mild pain	3 Very drowsy	2 Vomiting in last 1 h
3 Moderate pain	4 Asleep	
4 Severe pain		

postoperative radiography in the recovery room, to confirm correct placement of the catheters and to outline the likely route of spread of local anaesthetic solution.

Statistical significance was tested using one-way analysis of variance for morphine consumption data. The Kruskal–Wallis test was used for VAS data and chi-square test for scores assessed by nursing staff. Statistical significance was accepted when $P < 0.05$.

RESULTS

Twenty-two patients entered the study. One patient required mechanical ventilation after operation and the PCA device suffered malfunction during another case. Complete data were available therefore for 20 patients. Details of the patients' characteristics and of surgical procedure are given in table II.

Patients consumed less morphine while receiving intercostal bupivacaine than while receiving intercostal saline (table III). The 24-h morphine requirements of group A patients decreased by a mean (95% confidence limits) of 3.90 (−8.4, 16.2) mg for day 2 (saline) compared with day 1 (bupivacaine). The 24-h morphine requirements of group B patients decreased by a mean of 34.10 (13.0, 55.2) mg for day 2 (bupivacaine) compared with day 1 (saline) ($P = 0.01$).

TABLE II. *Details of patients and surgical procedure*

	Group A ($n = 10$)	Group B ($n = 10$)
Age (yr) (median (range))	60 (56–64)	57 (49–66)
Sex (M/F)	6/4	7/3
Weight (kg) (mean (95% CL))	65 (60–69)	63 (59–68)
Side of thoracotomy		
Right	4	7
Left	6	3
Procedure		
Segmental resection	1	3
Lobectomy	4	7
Pneumonectomy	2	
Instillation of cytotoxics	1	
Oesophageal surgery	2	

TABLE III. *Morphine consumption during each 24-h period of the study and over the total 48 h (mean (95% CL))*

	Morphine in 1st 24 h (mg)	Morphine in 2nd 24 h (mg)	Morphine per 24 h (mg)
Bupivacaine	33 (21–46)	25 (17–34)	29 (22–37)
Saline	59 (38–80)	30 (20–39)	44 (32–57)
P	0.03	0.44	0.04

TABLE IV. *Visual analogue scores of pain over the 48-h study period (median (interquartile limits))*

	VAS (mm)
Bupivacaine ($n = 20$)	27.0 (13.0–44.25)
Saline ($n = 20$)	38.5 (23.5–58.75)
P value	0.03

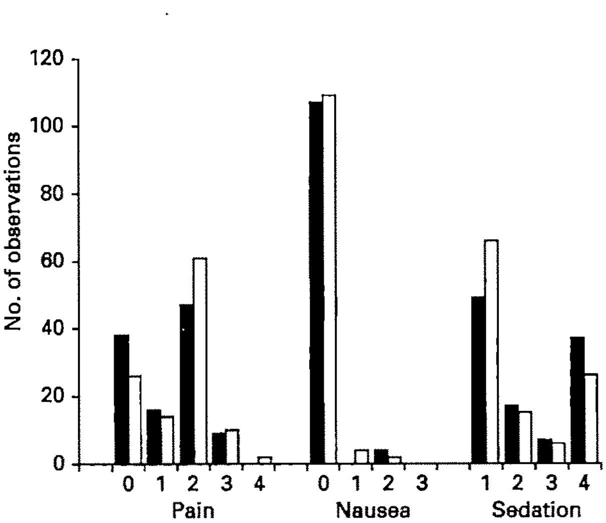


FIG. 1. Distribution of observations recorded by nursing staff for pain, nausea and sedation, after bupivacaine (■) or saline (□), using the system described in table I.

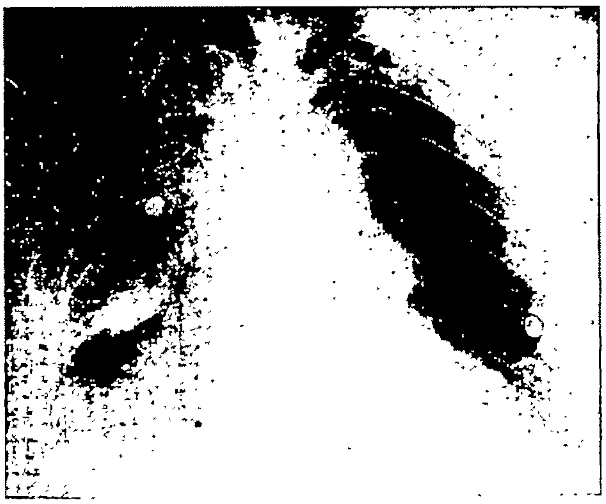


FIG. 2. Representative portable AP chest radiograph taken immediately after surgery, showing spread of contrast medium injected through intercostal catheters.

Patients recorded smaller visual analogue scores of pain while receiving bupivacaine (table IV).

Scores assessed by nursing staff for pain, sedation and nausea did not differ in patients receiving either bupivacaine or saline (fig. 1).

Radiography demonstrated spread of contrast medium along the intercostal space and the ipsilateral paravertebral space (fig. 2).

DISCUSSION

Administration of bupivacaine by the intercostal route reduced the requirement for morphine after thoracotomy. Individual requirements for postoperative analgesia vary greatly, but the crossover design of this study allowed each patient to act as his or her own control. Analgesic requirements would be expected to decrease over the 48-h period of the study, but this should affect both groups A and B similarly.

Patients recorded smaller visual analogue scores of pain while receiving bupivacaine. This suggests that patients were more comfortable with intercostal bupivacaine and self-administered morphine than with self-administered morphine alone.

There were no differences in the nursing assessment of degree of pain, sedation and nausea between patients when receiving bupivacaine or placebo. This may reflect the insensitive nature of the scoring systems used.

The radiographic demonstration of contrast medium in the paravertebral space suggests that paravertebral block contributed to the efficacy of this technique. It has been demonstrated previously that intercostal injections spread via the paravertebral space [3, 4, 6]. However, it should not be assumed that an intercostal injection of contrast medium and an intercostal infusion of bupivacaine behave similarly. Morphine consumption by patients during bupivacaine infusion was greater than would be expected (mean 29 mg, 95 % CL 22, 37 mg) if paravertebral block was significant. In a study of bupivacaine infused into the paravertebral space after thoracotomy, the mean requirement for papaveretum was 14 mg in the first 48 h [7]. Sources of pain after thoracotomy potentially covered by paravertebral but not by intercostal block include the ribs and costochondral joints, viscera and the chest drain site [8].

No patient in this study required treatment for hypotension or catheterization for urinary retention, which compares favourably with extradural analgesia [9]. The technique described here had the further attraction that placement of the catheters was performed under direct vision, increasing the incidence of correct positioning whilst also reducing the risks of injury to the lung and of intravascular placement.

Although the intercostal space is highly vascular, with rapid absorption of local anaesthetics [10], the dose of bupivacaine required for this technique ($25\ \mathrm{mg\ h^{-1}}$) is well below the recommended safety limit of $2\ \mathrm{mg\ kg^{-1}}$ in any 4-h period. Chan and colleagues [5] injected 0.5 % bupivacaine 10 ml with adrenaline 6-hourly through intercostal catheters. They studied six patients for 48 h after thoracotomy and found plasma concentrations of bupivacaine to be less than $4\ \mu\mathrm{g\ ml^{-1}}$.

We conclude that a continuous intercostal infusion of bupivacaine is associated with a low incidence of complications, and provides an effective adjunct to systemic opioids in the relief of pain after thoracotomy.

ACKNOWLEDGEMENTS

We thank Mr M. A. Turner and Mr A. Faichney of the Department of Cardiothoracic Surgery and Miss W. Fallon of Pharmacy for their help in this study.

REFERENCES

1. Loan WB, Dundee JW. The clinical assessment of pain. *Practitioner* 1967; 198: 759–768.
2. Moore DC. Intercostal nerve block for postoperative somatic pain following surgery of thorax and upper abdomen. *British Journal of Anaesthesia* 1975; 47: 284–286.
3. Mowbray A, Wong KKS, Murray JM. Intercostal catheterisation—an alternative approach to the paravertebral space. *Anaesthesia* 1987; 42: 958–961.
4. Crossley AW, Hosie HE. Radiographic study of intercostal nerve blockade in healthy volunteers. *British Journal of Anaesthesia* 1987; 59: 149–154.
5. Chan V, Chung F, Cheng DCH, Kirby TJ, Chung A, Sandler A. Continuous intercostal block for pain relief following thoracotomy—a new approach. *Canadian Journal of Anaesthesia* 1988; 35: S113–114.
6. Moore DC. Intercostal nerve block: spread of india ink injected to the rib's costal groove. *British Journal of Anaesthesia* 1981; 53: 325–329.
7. Sabanathan S, Mearns AJ, Bickford Smith PJ, Eng J, Berrisford RG, Bibby SR, Majid MR. Efficacy of continuous extrapleural intercostal nerve block on post-thoracotomy pain and pulmonary mechanics. *British Journal of Surgery* 1990; 77: 221–225.
8. Conacher ID. Pain relief after thoracotomy. *British Journal of Anaesthesia* 1990; 65: 806–812.
9. Matthews PJ, Govenden V. Comparison of continuous paravertebral and extradural infusions of bupivacaine for pain relief after thoracotomy. *British Journal of Anaesthesia* 1989; 62: 204–205.
10. Braid DP, Scott DB. The systemic absorption of local analgesic drugs. *British Journal of Anaesthesia* 1965; 37: 394–404.

British Journal of Anaesthesia 1993; 70: 511–514

MORPHINE-6-GLUCURONIDE DISPOSITION IN RENAL IMPAIRMENT

M. H. HANNA, F. D'COSTA, S. J. PEAT, C. FUNG, N. VENKAT, T. R. ZILKHA AND S. DAVIES

SUMMARY

Twelve patients with chronic renal failure (dialysis-dependent) and six with good renal function after renal transplantation received i.v. morphine-6-glucuronide (M6G) 30 $\mu g\ kg^{-1}$ as part of a standardized anaesthetic technique for minor surgery. Continuous peritoneal dialysis was commenced 6 h after M6G administration in six of the dialysis-dependent patients. Serum was sampled for up to 12 h and analysed for morphine and M6G by high pressure liquid chromatography. Morphine was not detected. Mean (SD) derived pharmacokinetic variables for the three groups (transplant, renally impaired non-dialysed and renally impaired dialysed, respectively) were: elimination half-life 2.14 (0.69) h, 27.10 (15.8) h, 17.33 (4.6) h; clearance 96.0 (34.9) ml min^{-1}, 10.57 (5.57) ml min^{-1}, 14.3 (6.2) ml min^{-1}; volume of distribution 0.19 (0.03) litre kg^{-1}, 0.25 (0.06) litre kg^{-1}, 0.27 (0.06) litre kg^{-1}. The elimination half-life was shorter ($P < 0.01$) and the clearance greater ($P < 0.01$) for the transplanted group compared with the dialysed and non-dialysed groups. Peritoneal dialysis for the second 6 h after drug administration had little effect on M6G disposition as assessed by comparison with data obtained from the non-dialysed group. (Br. J. Anaesth. 1993; **70**: 511–514)

KEY WORDS

Analgesics: morphine-6-glucuronide. Kidney: peritoneal dialysis, renal failure. Pharmacokinetics.

The morphine metabolite morphine-6-glucuronide (M6G) is a potent analgesic in animals [1–4] and man [5, 6]. Its analgesic action appears to be mediated via a mechanism similar to that proposed for morphine [2], but it has a greater potency, a longer duration of action and a smaller ED_{50}: LD_{50} ratio [1–4, 6].

There are large unexplained variations in clinical dose requirements and dynamic responses to morphine. This could be accounted for partly by factors such as age, disease, nature and severity of pain, and the use of concomitant medication [7]. Variations in response may also be secondary to interindividual variability in the pharmacokinetic properties of morphine and its 3- and 6-glucuronide metabolites [8]. Morphine-3-glucuronide (M3G) and M6G quickly attain plasma concentrations exceeding those of the parent drug after both single and multiple dosing with morphine, irrespective of the route of administration [9, 10]. The presence of active metabolites in such large quantities may further complicate the unpredictable pharmacodynamic response to administration of the parent drug.

Renal impairment does not significantly change morphine disposition when assessed by specific assays not subject to interference by the presence of metabolites [8, 11–15]. Increased concentrations of M6G and M3G after administration of morphine to these patients has been well documented [11, 13–15]. The nature of morphine glucuronide disposition in patients with renal impairment has considerable clinical implications and necessitates careful assessment.

Definition of the contribution of active metabolites to the therapeutic or toxic effects that occur after administration of the parent compound is difficult [16, 17]. In order to gain a clear understanding of this contribution, kinetic and dynamic investigations of the metabolite in the absence of the parent drug and in a clinically relevant setting are necessary. The present study is the first to investigate the pharmacokinetics of i.v. M6G in patients with functioning renal transplants and chronic renal impairment, and to examine the effect of peritoneal dialysis on its kinetic profile.

PATIENTS AND METHODS

After obtaining Ethics Committee approval and written informed consent, we studied 18 patients with chronic renal impairment presenting for minor surgery under general anaesthesia. Six had good renal function after renal transplantation and 12 were dependent on peritoneal dialysis. Dialysis-dependent patients were allocated randomly to two groups: those in group 1 were not dialysed during the study; those allocated to group 2 underwent continuous peritoneal dialysis (hourly 1-litre cycles) commencing at 6 h after administration of M6G and continuing for the remainder of the study. All patients were fasted for 6 h before operation and i.v.

M. H. HANNA, F.R.C.ANAES.; F. D'COSTA, F.R.C.ANAES.; S. J. PEAT, B.SC., F.R.C.ANAES.; C. FUNG, PH.D.; N. VENKAT, F.R.C.ANAES.; T. R. ZILKHA, F.R.C.ANAES.; S. DAVIES*, F.R.C.ANAES.; Pain Relief Research Unit, Department of Anaesthesia, King's College Hospital, Denmark Hill, London SE5 9RS. Accepted for Publication: December 15, 1992.

Correspondence to M.H.H.

*Present address: Department of Anaesthesia, Neath General Hospital, West Glamorgan, Wales.

fluids were not administered. Non-invasive cardiorespiratory monitoring (automated oscillometer and pulse oximeter) and venous cannulation were performed before induction of anaesthesia and maintained throughout the study. All patients received i.v. M6G 30 $\mu g\ kg^{-1}$ over 4 min at induction of anaesthesia as part of a standardized anaesthetic technique. Anaesthesia was induced using propofol 2.5 $mg\ kg^{-1}$ and patients were subsequently allowed to breathe spontaneously a mixture of 50 % nitrous oxide and 1–2 % isoflurane in oxygen. Venous blood samples were taken from a cannula in the opposite limb before, and at 5, 10, 15, 20, 40, 60, 80, 120, 160, 200, 240, 280, 320 and 360 min after administration of M6G, then hourly for another 6 h.

The samples were separated by centrifugation and the supernatant stored at −20 °C until analysis for morphine and M6G by high pressure liquid chromatography with electrochemical detection in accordance with an assay technique described previously [18, 19]. Calibration curves were constructed daily for morphine and M6G using standards obtained from Evans Medical (morphine) and Ultrafine Chemicals (M6G). These were linear with coefficients greater than 0.997. Each sample was analysed once. The lower limit of detection was 1 $ng\ ml^{-1}$ for both morphine and M6G.

Derived pharmacokinetic parameters were calculated by weighted, interactive, computer-assisted non-linear regression analysis [20, 21] using a two-compartment model for all patients. Pharmacokinetic and biochemical data obtained for the three groups (transplanted, renally impaired and renally impaired dialysed) were compared using the Mann–Whitney U test.

TABLE I. *Pre-trial data for patients entered into the study. Patients with renal transplants had significantly smaller pre-trial creatinine concentrations than those who were dialysis-dependent* ($P < 0.01$ *for patients allocated to the dialysis group and non-dialysis groups*) (*mean* (SD) [*range*])

	Age (yr)	Weight (kg)	Creatinine (mmol $litre^{-1}$)
Transplant	45.90	86.67 (20.83)	130.5 (26.0)
($n = 6$)	[33.0–56.25]	[63.5–113.2]	[103–176]
Non-dialysed	48.68	73.57 (12.28)	696.7 (296.4)
($n = 6$)	[18.5–66.83]	[53.0–86.0]	[206–983]
Dialysed	58.87	73.75 (15.24)	660.7 (361.1)
($n = 6$)	[34.17–69.67]	[57.0–101]	[325–1103]

RESULTS

Of the 12 patients with dialysis-dependent renal impairment, six were allocated to group 1 (non-dialysed) and six to group 2 (dialysed). The three groups were similar in age, weight and serum albumin concentrations (table I). The serum creatinine concentrations for both group 1 and group 2 were significantly greater than those for the transplanted group ($P < 0.01$ in each case) (table I). The patients were receiving a wide variety of medication including vitamins, antibiotics, alfacalciferol, insulin, vasodilators, H_2 antagonists, phosphate binding agents, antibiotics, antihypertensives, antidepressants and calcium carbonate. Those with functioning transplants were receiving immunosuppressive therapy (azathioprine and prednisolone with or without cyclosporin). The nature and duration of surgery was similar in all three groups, consisting of vascular access surgery and insertion and removal of peritoneal dialysis catheters. One patient (in the transplant group) underwent repair of a small incisional hernia. The maximum duration of surgery was 20 min. Oxygen saturation remained greater than 95 % in all patients throughout the study. Arterial pressure, heart rate and ventilatory frequency recorded for patients in the three groups were similar and remained within a clinically acceptable range of values. There were no adverse reactions in any patient.

Morphine was not detected in any samples. The elimination half-lives obtained in both the non-dialysed and dialysed groups were significantly longer than those obtained for the transplant group ($P < 0.01$ in each case) and the values obtained for clearance were significantly smaller ($P < 0.01$ in each case) (table II). The volumes of distribution were similar in all three groups (table II).

Peritoneal dialysis (started 6 h after administration of M6G) had little effect on pharmacokinetic parameters obtained for M6G as assessed by comparison with data obtained from the non-dialysed group.

DISCUSSION

There has been increasing debate on the disposition and metabolism of morphine in patients with renal insufficiency and its association with adverse reactions [22]. Morphine disposition is not usually

TABLE II. *Pharmacokinetic data* (*mean* (SD) [*range*]) *for three groups of patients given i.v. M6G 30* $\mu g\ kg^{-1}$. *In patients with renal transplants M6G clearance was greater and elimination half-life longer than that obtained in either the dialysed or non-dialysed groups* ($P < 0.01$). AUC_{0-6} = *Area under the concentration time curve for the first 6 h*; AUC_{0-12} = *area under the concentration time curve for the first 12 h*; Cl = *clearance*; V*d* = *volume of distribution*; $T_{\frac{1}{2}}^{\beta}$ = *elimination half- life*

	AUC_{0-6} (ng h ml^{-1})	AUC_{0-12} (ng h ml^{-1})	*Cl* (ml min^{-1})	*V*d (litre kg^{-1})	$T_{\frac{1}{2}}^{\beta}$ (h)
Transplant	411.9 (118.7)	501.6 (208.9)	96.0 (34.9)	0.19 (0.03)	2.14 (0.69)
($n = 6$)	[289.6–611.2]	[317.1–769.3]	[54.2–145.2]	[0.14–0.24]	[1.51–3.30]
Non-dialysed	691.1 (120.5)	1228.25 (232.1)	10.6 (5.6)	0.25 (0.06)	27.10 (15.83)
($n = 6$)	[534.7–845.3]	[966.03–1582.71]	[3.9–17.6]	[0.18–0.35]	[9.38–50.83]
Dialysed	619.2 (96.9)	1086.20 (172.8)	14.3 (6.2)	0.27 (0.06)	17.33 (4.63)
($n = 6$)	[499.5–730.2]	[799.6–1337.1]	[6.6–25.0]	[0.21–0.37]	[10.34–24.28]

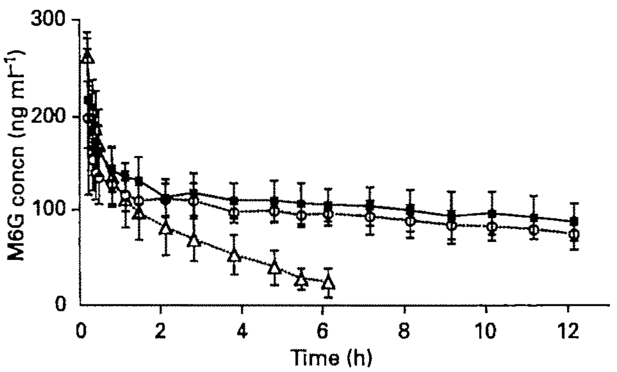


FIG. 1. Mean (SD) concentration–time curves for M6G in transplanted patients (Δ), dialysis-dependent patients not dialysed during the study (■) and dialysis-dependent patients dialysed from 6 to 12 h after administration of M6G (○).

altered in uraemic patients [8, 12, 13], but clinical data indicate that patients with renal failure are particularly susceptible to the toxic effects of morphine, and may have small dose requirements for analgesia [2, 8, 15, 23–25]. Hypotheses advanced to explain this include systemic metabolite deconjugation, biliary excretion of glucuronides and deconjugation by gut flora, increased enterohepatic circulation of morphine and accumulation of large quantities of active metabolites [2, 8, 15, 24, 26]. The pharmacokinetic profile of M6G as a morphine metabolite (M6Gi) has been investigated in patients with renal impairment, and a prolonged half-life demonstrated [11, 15, 25].

The absence of morphine in serum after the administration of M6G presented here excludes systemic deconjugation (or enteral deconjugation and reabsorption) sufficient to generate detectable quantities of the parent drug. The pharmacokinetic data presented here, relating to direct administration of M6G, have demonstrated that renal impairment was associated with a considerable delay in removal of M6G from the plasma compartments (fig. 1). Further analysis of the data demonstrates that renal impairment was associated with prolongation of the M6G terminal elimination half-life ($T_{\frac{1}{2}}^{\beta}$) and a reduction in M6G clearance (Cl) with no change in volume of distribution (Vd). Although Vd and Cl are independent terms, they are determinants of $T_{\frac{1}{2}}^{\beta}$ as follows:

$$T_{\frac{1}{2}}^{\beta} = \frac{0.69\ V\mathrm{d}}{Cl}$$

Thus the prolongation of M6G $T_{\frac{1}{2}}^{\beta}$ for patients with renal impairment is a direct reflection of reduced clearance, indicating that clearance is highly dependent on a functioning kidney. It may be concluded that accumulation of M6Gi in patients with renal impairment given morphine is secondary to the pharmacokinetic characteristics of the metabolite rather than to those of the parent drug. This confirms a previous case report [5].

Morphine and M6G bind to mu receptors stereospecifically with high affinity, although they have different affinities for the mu subtypes [2–4, 26]. Receptor binding in the biophase, and the consequent clinical effects, are subject to a complex array of competing influences ranging from the physicochemical characteristics of the drug to physiological changes in the patient. It is, nonetheless, curious that we did not observe prolonged respiratory depression, in view of the relatively large concentrations attained. In patients with renal impairment, persistently increased concentrations of systemic M6Gi after multiple dosing with morphine may be expected to facilitate entry of M6Gi to the CSF and biophase, and M6G elimination from the CSF compartment appears to occur more slowly than that of the parent drug [6]. Central accumulation of M6Gi could therefore explain toxicity occurring at relatively small systemic concentrations. Alterations in the response of patients secondary to uraemia, drug interactions, increased blood–brain permeability, changes in protein binding and receptor affinity, or the presence of other opioids must also be considered.

The pharmacokinetic parameters obtained in the transplant group of this study were similar to those reported for normal (awake) volunteers [27, 28], demonstrating that patients with good renal function after transplantation are able to clear M6G effectively. Comparison of the data obtained in these two studies suggests that the effect of general anaesthesia on M6G disposition in patients with functioning renal transplants is minimal. The findings of an investigation into the effect of general anaesthesia on the elimination of morphine and its glucuronides in healthy patients implied that anaesthesia delayed M6Gi excretion, possibly secondary to a reduction in renal blood flow [29]. The apparent discrepancy between these results and the findings of the present study may reflect the differing responses of the normal and transplanted kidney to the stress of anaesthesia and surgery, possibly secondary to the lack of graft innervation and failure to modulate renal blood flow.

Six hours continuous peritoneal dialysis had little effect on M6G disposition. M6G has a low Vd ($<$ 0.5 litre kg^{-1}) and, in patients with renal impairment, a prolonged $T_{\frac{1}{2}}^{\beta}$, suggesting that, providing it crosses the peritoneal membrane easily, it is removed efficiently by dialysis. Our results, and data from a previous case report [2] suggest that this is not so. Drug elimination by peritoneal dialysis is inefficient if the dialysate flow rate is low, if its volume of distribution in the dialysate is small compared with its total volume of distribution, or if the contribution of peritoneal dialysis to total body clearance is insignificant because of the simultaneous presence of other routes of removal [30]. Investigation of the physicochemical characteristics of M6G, particularly its degree of protein binding and ionization, may help to explain its pharmacokinetic profile in dialysis-dependent patients.

REFERENCES

1. Shimomura K, Kamata O, Ueki S, Ida S, Oguri K, Yoshimura H, Tsukamoto H. Analgesic effects of morphine glucuronides. *Tohoku Journal of Experimental Medicine* 1971; 105: 45–52.
2. Paul D, Standifer KM, Inturrissi CE, Pasternak GW. Pharmacological characterization of morphine-6 beta-glucuronide, a very potent morphine metabolite. *Journal of Pharmacology and Experimental Therapeutics* 1989; 251: 477–483.

3. Frances B, Gout R, Campistron G, Panconi E, Cros J. Morphine-6-glucuronide is more mu-selective and potent in analgesic tests than morphine. *Progress in Clinical and Biological Research* 1990; **328**: 477–480.
4. Abbott FV, Palmour RM. Morphine-6-glucuronide: analgesic effects and receptor binding profile in rats. *Life Science* 1988; **43**: 1685–1695.
5. Osborne RJ, Joel SP, Trew D, Slevin M. Analgesic activity of morphine 6 glucuronide. *Lancet* 1988; **1**: 828.
6. Hanna MH, Peat SJ, Woodham M, Knibb A, Fung C. Analgesic efficacy and CSF pharmacokinetics of intrathecal morphine 6 glucuronide: comparison with morphine. *British Journal of Anaesthesia* 1990; **64**: 547–550.
7. McQuay HJ, Carroll D, Faura CC, Gavaghan DJ, Hand CW, Moore RA. Oral morphine in cancer pain: influences on morphine and metabolite concentration. *Clinical Pharmacology and Therapeutics* 1990; **48**: 236–244.
8. Chan GLC, Matzke GR. Effects of renal insufficiency on the pharmacokinetics and pharmacodynamics of opioid analgesics. *Drug Intelligence and Clinical Pharmacy* 1987; **21**: 773–783.
9. Sawe J, Svensson JO, Rane A. Morphine metabolism in cancer patients on increasing oral doses—no evidence for autoinduction or dose dependence. *British Journal of Clinical Pharmacology* 1983; **16**: 85–93.
10. Osborne RJ, Joel SP, Trew D, Slevin M. Morphine and metabolite behaviour after different routes of morphine administration: Demonstration of the importance of the active metabolite morphine-6-glucuronide. *Clinical Pharmacology and Therapeutics* 1990; **47**: 12–19.
11. Sear JW, Hand CW, Moore RA, McQuay HJ. Studies on morphine disposition: Influence of renal failure on the kinetics of morphine and its metabolites. *British Journal of Anaesthesia* 1989; **62**: 28–32.
12. Wolff J, Bigler D, Christensen CB, Rasmussen SN, Andersen HB, Tonnesen KH. Influence of renal function on the elimination of morphine and morphine glucuronides. *European Journal of Clinical Pharmacology* 1988; **34**: 353–357.
13. Woolner DF, Winter D, Frendin TJ, Begg EJ, Lynn KL, Wright GJ. Renal failure does not impair the metabolism of morphine. *British Journal of Clinical Pharmacology* 1986; **22**: 55–59.
14. Aitkenhead AR, Vater M, Achola K, Cooper CMS, Smith G. Pharmacokinetics of single-dose i.v. morphine in normal volunteers and patients with end-stage renal failure. *British Journal of Anaesthesia* 1984; **56**: 813–819.
15. Peterson GM, Randall CT, Paterson J. Plasma levels of morphine and morphine glucuronides in the treatment of cancer pain: relationship to renal function and route of administration. *European Journal of Clinical Pharmacology* 1990; **38**: 121–124.
16. Garattini S. Active drug metabolites. An overview of their relevance in clinical pharmacokinetics. *Clinical Pharmacokinetics* 1985; **10**: 216–227.
17. Pang KS. A review of metabolite kinetics. *Journal of Pharmacokinetics and Biopharmaceutics* 1985; **13**: 633–662.
18. Svensson JO. Determination of morphine, morphine-6-glucuronide and normorphine in plasma and urine with high performance liquid chromatography. *Journal of Chromatography* 1986; **230**: 427–432.
19. Joel SP, Osborne RJ, Slevin ML. An improved method for the simultaneous determination of morphine and its principal glucuronide metabolites. *Journal of Chromatography* 1988; **430**: 394–399.
20. Johnston A. SIMP, A basic computer program for non linear curve fitting. *Journal of Pharmacological Methods* 1985; **14**: 323–329.
21. Johnston A, Woolard RC. STRIPE: An interactive computer program for the analysis of drug pharmacokinetics. *Journal of Pharmacological Methods* 1983; **9**: 193–200.
22. Sear JW. Drug biotransformation by the kidney: How important is it, and how much do we really know? *British Journal of Anaesthesia* 1991; **67**: 369–372.
23. Don HF, Dieppa RA, Taylor P. Narcotic analgesics in anuric patients. *Anesthesiology* 1975; **42**: 745–747.
24. Osborne RJ, Joel SP, Slevin ML. Morphine intoxication in renal failure: the role of morphine 6 glucuronide. *British Medical Journal* 1986; **292**: 1548–1549.
25. Bodd E, Jacobsen D, Lund E, Ripel A, Morland J, Wiik-Larsen E. Morphine-6-glucuronide might mediate the prolonged opioid effect of morphine in acute renal failure. *Human and Experimental Toxicology* 1990; **9**: 317–321.
26. Hucks D, Thompson PI, McLoughlin L, Joel SP, Patel N, Grossman A, Rees LH, Slevin ML. Explanation at the opioid receptor level for the differing toxicity of morphine and morphine 6-glucuronide. *British Journal of Cancer* 1992; **65**: 122–126.
27. Hanna MH, Peat SJ, Knibb AA, Fung C. Disposition of morphine 6 glucuronide and morphine in healthy volunteers. *British Journal of Anaesthesia* 1991; **66**: 103–107.
28. Hanna MH. Toxicity and pharmacokinetics of morphine and morphine-6-glucuronide. *British Journal of Anaesthesia* 1991; **67**: 363.
29. Sear JW, Hand CW, Moore RA, McQuay HJ. Studies on morphine disposition: influence of general anaesthesia on plasma concentrations of morphine and its metabolites. *British Journal of Anaesthesia* 1989; **62**: 22–27.
30. Keller E. Peritoneal kinetics of different drugs. *Clinical Nephrology* 1988; **30** (Suppl. 1): s24–8.

British Journal of Anaesthesia 1993; **70**: 515–518

PARTIAL REVERSAL OF THE EFFECTS OF EXTRADURAL CLONIDINE BY ORAL YOHIMBINE IN POSTOPERATIVE PATIENTS

N. LIU, F. BONNET, L. DELAUNAY, N. KERMAREC AND G. D'HONNEUR

SUMMARY

Extradural clonidine produces analgesia, with sedation, hypotension and bradycardia, in postoperative patients. This study assessed if oral yohimbine would reverse these side effects. We studied 30 ASA I–II patients undergoing orthopaedic surgery. After operation they were allocated randomly to three groups to receive placebo, extradural clonidine 450 μg or extradural clonidine 450 μg plus oral yohimbine 16 mg. Pain score was measured on a visual analogue scale (VAS); sedation was assessed on a simple scale graded from 0 (awake and alert) to 3 (deeply sedated, awakening after tactile stimulations) and heart rate and arterial pressure were monitored for 5 h. Yohimbine reversed the sedation induced by extradural clonidine, but also shortened the duration of analgesia (31 (SD 15) min, 186 (72) min and 126 (52) min in the placebo, extradural clonidine and extradural clonidine+yohimbine groups, respectively) ($P < 0.05$), and did not reduce the hypotension and bradycardia related to clonidine administration. These results suggest that alpha$_2$ adrenoceptors are mediators of the sedation induced by clonidine and that the haemodynamic effects are not related to stimulation of supraspinal alpha$_2$ receptors. (Br. J. Anaesth. 1993; **70**: 515–518)

KEY WORDS

Anaesthetic techniques: extradural. Pain: postoperative. Sympathetic nervous system, alpha$_2$ adrenergic agonists: clonidine; alpha$_2$ adrenergic antagonists: yohimbine.

Clonidine produces analgesia in laboratory animals and in postoperative patients via alpha$_2$ adrenoceptors located in the dorsal horn of the spinal cord [1–4]. Systemic absorption of clonidine occurs after extradural administration and is considered responsible for the side effects of hypotension, bradycardia and sedation which may limit its use for postoperative analgesia [1, 2, 5–7]. Yohimbine is an alpha$_2$ adrenoceptor antagonist which reverses both analgesia and side effects induced by alpha$_2$ agonists in animals [3, 4, 8, 9]. Naloxone has been reported to reverse side effects induced by extradural morphine while analgesia was unchanged, because of a favourable balance between agonist and antagonist at the level of the spinal cord while antagonist effectively competes with agonist at the other sites of action responsible for side effects [10]. It may be postulated that the oral administration of yohimbine might reverse the side effects of extradural clonidine while analgesia would be maintained. This study, performed in postoperative patients, was designed to evaluate this hypothesis.

PATIENTS AND METHODS

After obtaining institutional Ethics Committee approval and informed consent, we studied 30 ASA I patients undergoing orthopaedic surgery. Patients who were receiving alpha$_2$ adrenoceptor agonists, neuroleptics, tricyclic antidepressants or beta blocking agents were excluded from the study.

Surgery of the lower limbs was performed under extradural anaesthesia using 0.5% bupivacaine. After operation, in the recovery room, patients were allocated randomly to three groups when they had recovered from local anaesthetic block and complained of pain. In the first group, patients received an oral placebo and 10 ml of an extradural isotonic saline solution, the second group received an oral placebo and extradural clonidine 450 μg diluted in 10 ml of an isotonic solution and the third group received the same dose of extradural clonidine and yohimbine 16 mg orally. The dose of oral yohimbine was determined from a previous open study, as the minimal dose necessary to reverse sedation induced by extradural clonidine 450 μg.

Patients rated their pain using a visual analogue scale (VAS) graded from 0 (no pain) to 10 (maximum pain) [11] before administration of the test drugs, then every 15 min for the first 1 h and then every 1 h for 6 h. At the first complaint of pain after extradural administration of clonidine or placebo, patients were given paracetamol 500 mg i.v. VAS scores after paracetamol were excluded from analysis and comparisons between groups. We determined the duration of action of extradural clonidine or placebo by the time elapsed between clonidine or placebo administration and the first paracetamol injection.

Sedation was measured by a blinded observer on a scale graded as follows: 0 = fully conscious; 1 = sleepy awakening spontaneously; 2 = sleepy awak-

---

N. Liu, M.D.; F. Bonnet, M.D.; L. Delaunay, M.D.; N. Kermarec, M.D.; G. D'Honneur, M.D.; Département d'Anesthésie Réanimation, Hôpital Henri Mondor, 51, avenue du Maréchal de Lattre de Tassigny, 94010 Créteil, France. Accepted for Publication: November 11, 1992.

TABLE I. *Patient data (mean (range or* SD*))*

	Sex (M/F)	Age (yr)	Weight (kg)	Height (cm)
Placebo	5/5	49 (18–78)	70 (13)	169 (10)
Clonidine	5/5	43 (18–56)	72 (15)	169 (9)
Clonidine + yohimbine	4/6	42 (21–71)	67 (12)	168 (10)

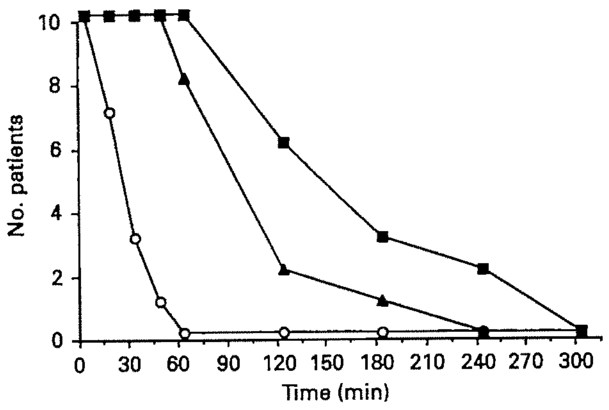


FIG. 1. Number of patients who did not require further analgesia after extradural injection ($n = 10$ in each group). $P < 0.05$ for clonidine (■) and clonidine + yohimbine (▲) groups compared with placebo group (○).

ening after verbal stimulations; 3 = drowsy awakening after tactile stimulations; 4 = comatose. Patients were evaluated for sedation simultaneously with VAS measurements. Arterial pressure and heart rate were measured before and every 5 min throughout the study using an automatic oscillotonometer (Dinamap, Critikon).

Values are expressed as mean (SD). Statistical analysis used a two-way ANOVA for repeated measures and Student's *t* test. Duration of analgesia were compared using the Kaplan Meier method and a log-rank test. Differences were considered significant when $P < 0.05$.

RESULTS

Patient data were comparable in the three groups (table I). Duration of analgesia was prolonged significantly in patients receiving clonidine or clonidine + yohimbine compared with placebo (31 (SD 15) min in the placebo group, 186 (72) min in the clonidine group and 126 (52) min in the clonidine + yohimbine group) ($P < 0.05$). The difference was also statistically significant between patients receiving extradural clonidine and extradural clonidine with oral yohimbine. After extradural administration, patients in the placebo group required i.v. paracetamol more rapidly than in the clonidine or clonidine + yohimbine groups (fig. 1). VAS values were also significantly smaller in patients receiving clonidine with or without yohimbine over the first 2 h (fig. 2). Two hours after the extradural injection, all the patients in the placebo group and eight of 10 patients in the clonidine + yohimbine group had been given i.v. paracetamol and were excluded from comparative analysis of the VAS scores.

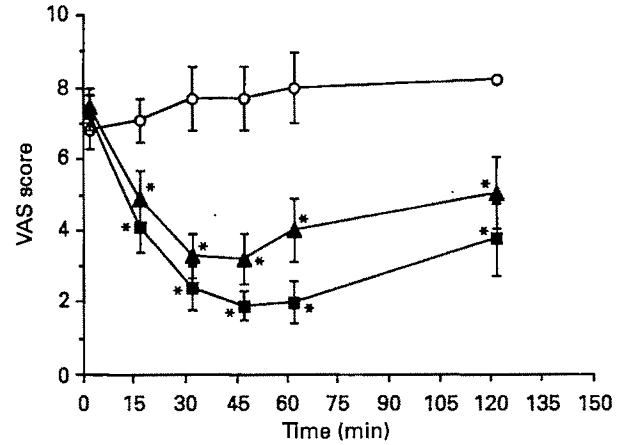


FIG. 2. Changes in VAS scores in the three groups of patients over the first 120 min. ■ = Clonidine; ▲ = clonidine + yohimbine; ○ = placebo. *$P < 0.05$ compared with placebo.

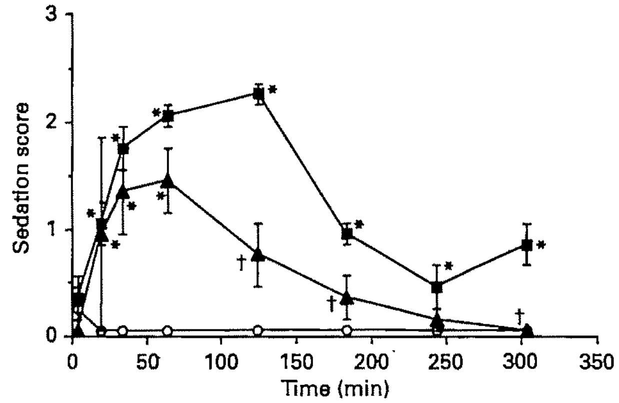


FIG. 3. Sedation scores in the three groups of patients. $P < 0.05$: * compared with placebo (○); † compared with clonidine (■). ▲ = Clonidine + yohimbine.

Significantly greater sedation scores were noticed in the clonidine group compared with placebo (fig. 3). The addition of oral yohimbine partly reversed ($P < 0.05$) sedation induced by clonidine (fig. 3). Significant decreases in arterial pressure and heart rate were noticed in patients who received extradural clonidine (figs 4, 5). Oral yohimbine had no significant effect on hypotension or bradycardia induced by extradural clonidine. Nevertheless, none of the patients in this study required treatment for hypotension or bradycardia.

DISCUSSION

We have shown that the oral administration of yohimbine partly reversed not only sedation induced by extradural clonidine, but also analgesia; however, it failed to alter significantly the changes in arterial pressure and heart rate at the doses of clonidine used. Clonidine-induced sedation is thought to be mediated by stimulation of alpha$_2$ adrenoceptors in the locus coeruleus and is reversed by yohimbine in animals [12]. In veterinary practice, yohimbine is commonly used to reverse sedation induced by the related compound, xylazine [9, 13–15].

After extradural administration, clonidine may reach supraspinal sites responsible for sedation, by

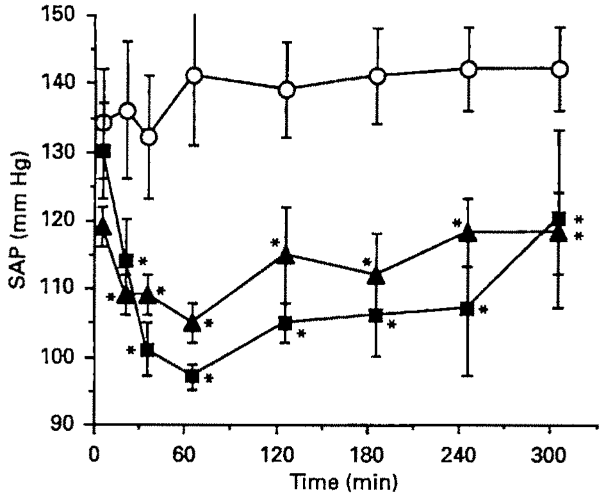


FIG. 4. Changes in systolic arterial pressure in the three groups. ■ = Clonidine; ▲ = clonidine+yohimbine; ○ = placebo. $*P < 0.05$ compared with placebo.

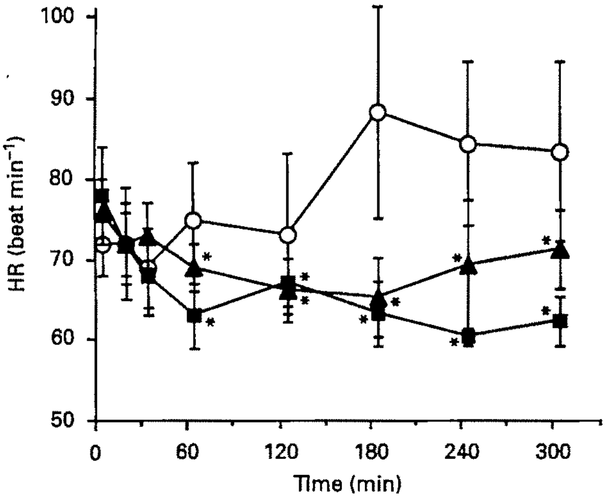


FIG. 5. Changes in heart rate (HR) in the three groups. ■ = Clonidine; ▲ = clonidine+yohimbine; ○ = placebo. $*P < 0.05$ compared with placebo.

systemic absorption; the peak plasma concentration occurs within 5–10 min [16], while sedation is observed within 15 min [5]. Clonidine may also reach supraspinal centres by cephalad migration through the CSF [17]. No excessive sedation was noticed in our patients after extradural administration of clonidine. Nevertheless, sedation induced by clonidine may occasionally induce snoring and hypoxaemia [18] and oral yohimbine easily reversed sedation in these individuals.

In the present study, clonidine-induced analgesia was also reversed partly by yohimbine, the effect being seen more on duration of analgesia, rather than its quality. Early VAS scores were comparable in those patients who received extradural clonidine and those who received extradural clonidine and oral yohimbine. However, the time from extradural injection of clonidine to supplementary analgesic demand was shorter in those patients given oral yohimbine. We speculate that, in the spinal cord, the ratio of concentrations between clonidine and yohimbine may have initially favoured clonidine, which rapidly crosses the dura mater after extradural administration. Later, this ratio may have changed, as systemic absorption of clonidine occurred and oral yohimbine reached the spinal cord alpha$_2$ receptors, shifting clonidine from its binding sites. Reversal of extradural clonidine-induced analgesia also depends on the respective doses of clonidine and yohimbine administered. In this study, the dose of yohimbine was determined from a previous open study in which yohimbine 16 mg seemed to be the minimal dose which reversed the sedation of clonidine 450 µg.

Hypotension and bradycardia related to extradural clonidine administration were not modified by oral yohimbine. The mechanism of the effect of clonidine on arterial pressure is complex. Clonidine produces hypotension by inhibition of the nucleus reticularis lateralis located in the ventrolateral medulla oblongata [19, 20]; it also directly inhibits sympathetic preganglionic neurones [21] and exerts a peripherally mediated vasoconstrictive effect [12]. The resultant action is a biphasic dose–response on arterial pressure, with a reduction at small doses partly corrected at large doses [2, 22]. In addition, several studies suggest that the supraspinal mechanism of action of clonidine on arterial pressure is mediated mainly by imidazoline receptors and not by alpha$_2$ adrenoceptors [22]. Indeed, intracisternal yohimbine has been reported not to reverse the hypotensive effect of clonidine or its inhibition of the nucleus reticularis lateralis [22]. Solomon, Brody and Gebhart have shown that the depressive effect produced by intrathecal clonidine in rats is prevented by a 10-fold greater dose of intrathecal yohimbine, but not altered by an equivalent dose of i.v. yohimbine [23]. A direct inhibition of sympathetic neurones may also play a role in the cardiovascular effect of spinally administered clonidine. This hypothesis is supported by the observation that hypotension is more marked after thoracic than lumbar extradural administration of clonidine in humans [24].

In conclusion, we found that sedation but not the haemodynamic effect of extradural clonidine was reversed by yohimbine in postoperative patients strengthening the hypothesis that the sedation is mediated by stimulation of supraspinal alpha$_2$ receptors. Yohimbine may be useful if excessive sedation leading to respiratory depression and hypoxaemia is observed in patients given clonidine for postoperative analgesia.

REFERENCES

1. Bonnet F, Boico O, Rostaing S, Saada M, Loriferne JF, Touboul C, Abhay K, Ghignone M. Postoperative analgesia with extradural clonidine. *British Journal of Anaesthesia* 1989; **63**: 93–96.
2. Eisenach JC, Lysak SZ, Viscomi CM. Epidural clonidine analgesia following surgery: Phase I. *Anesthesiology* 1989; **71**: 640–646.
3. Murata K, Nakagawa I, Kumeta Y, Kitahata LM, Collins JG. Intrathecal clonidine suppresses noxiously evoked activity of spinal wide dynamic range neurons in cats. *Anesthesia and Analgesia* 1989; **69**: 185–191.
4. Ossipov MH, Suarez LJ, Spaulding TC. A comparison of the

antinociceptive and behavioral effects of intrathecally administered opiates, α2 adrenergic agonists, and local anesthetics in mice and rats. *Anesthesia and Analgesia* 1988; **67**: 616–624.

5. Bonnet F, Boico O, Rostaing S, Loriferne JF, Saada M. Clonidine-induced analgesia in postoperative patients: epidural versus intramuscular administration. *Anesthesiology* 1990; **72**: 423–427.
6. Mendez R, Eisenach JC, Kashtan K. Epidural clonidine analgesia after cesarean section. *Anesthesiology* 1990; **73**: 848–852.
7. Carabine UA, Milligan KR, Mulholland D, Moore J. Extradural clonidine infusions for analgesia after total hip replacement. *British Journal of Anaesthesia* 1992; **68**: 338–343.
8. Hatch RC, Booth NH, Kitzman DVM, Wallner BM, Clark JD. Antagonism of ketamine anesthesia in cats by 4-aminopyridine and yohimbine. *American Journal of Veterinary Research* 1982; **44**: 417–423.
9. Kitzman DVM, Booth NH, Hatch RC, Wallner BM. Antagonism of xylazine sedation by 4-aminopyridine and yohimbine in cattle. *American Journal of Veterinary Research* 1982; **44**: 2165–2169.
10. Rawal N, Schott V, Dahlström R, Inturisi CE, Tandon B, Sjostrand U, Wennhager M. Influence of naloxone infusion on analgesia and respiratory depression following epidural morphine. *Anesthesiology* 1986; **64**: 194–201.
11. Huskisson EC. Measurement of pain. *Lancet* 1974; **2**: 1127–1131.
12. Timmermans PBMWM, Van Zwieten PA. Postsynaptic α1 and α2 adrenoreceptors in the circulatory system of the pithed rat: selective stimulation of the α2 type by B-HGT 933. *European Journal of Pharmacology* 1980; **63**: 199–202.
13. Hsu WH, Shulaw WP. Effect of yohimbine on xylazine-induced immobilization in white-tailed deer. *Journal of the American Veterinary Association* 1984; **185**: 1301–1303.
14. Jessup DA, Jones K, Mohr R, Kucera T. Yohimbine antagonism to xylazine in free-ranging mule deer and desert bighorn sheep. *Journal of the American Veterinary Association* 1985; **187**: 1251–1253.
15. Hatch RC, Booth NH, Clark JD, Crawford LM, Kitzman DVM, Wallner BM. Antagonism of xylazine sedation in dogs by 4-aminopyridine and yohimbine. *American Journal of Veterinary Research* 1982; **44**: 1009–1014.
16. Van Essen EJ, Bovill SG, Ploeger EJ, Houben JJG. Pharmacokinetics of clonidine after epidural administration in surgical patients. Lack of correlation between plasma concentration and analgesia and blood pressure changes. *Acta Anaesthesiologica Scandinavica* 1992; **36**: 300–304.
17. Post C, Gordh T, Minor BG, Archer T, Freedman J. Antinociceptive effects and spinal cord concentrations after intrathecal injections of guanfacine or clonidine in the rats. *Anesthesia and Analgesia* 1987; **66**: 317–324.
18. Huntoon M, Eisenach JC, Boese P. Epidural clonidine after cesarean section. Appropriate dose and effect of prior local anesthetic. *Anesthesiology* 1992; **76**: 187–193.
19. Bricca G, Dontenwill M, Moliness A, Feldman J, Belcourt A, Bousquet P. Evidence for the existence of an homogeneous population of imidazoline receptors in the human brainstem. *European Journal of Pharmacology* 1988; **50**: 401–402.
20. Ernsberger P, Meeley MO, Mann JJ, Reis DJ. Clonidine binds to imidazoline binding sites as well as alpha 2 adrenoreceptors in the ventrolateral medulla. *European Journal of Pharmacology* 1987; **134**: 1–13.
21. Guyenet PG, Cabot JH. Inhibition of sympathetic preganglionic neurons by catecholamines and clonidine mediation by an adrenergic receptor. *Journal of Neuroscience* 1981; **1**: 908–917.
22. Tibirica E, Feldman J, Mermet C, Gonon F, Bousquet P. An imidazoline specific mechanism for the hypotensive effect of clonidine: a study with yohimbine and idazoxan. *Journal of Pharmacology and Experimental Therapeutics* 1991; **256**: 606–613.
23. Solomon RE, Brody JM, Gebhart GF. Pharmacological characterization of alpha adrenoceptors involved in the antinociceptive and cardiovascular effect of intrathecally administered clonidine. *Journal of Pharmacology and Experimental Therapeutics* 1989; **251**: 27–38.
24. Eisenach JC, Tong C. Site of hemodynamic effects of intrathecal α2 adrenergic agonists. *Anesthesiology* 1991; **74**: 766–771.

British Journal of Anaesthesia 1993; **70**: 519–521

THE PRESSOR RESPONSE TO VENOUS CANNULATION: ATTENUATION BY PRIOR INFILTRATION WITH LOCAL ANAESTHETIC

B. T. LANGHAM AND D. A. HARRISON

SUMMARY

We have compared the cardiovascular response to insertion of an 18-gauge venous cannula in 40 healthy patients. In 20 of the patients, cannulation was preceded by infiltration of local anaesthetic. Both rate–pressure product and mean arterial pressure increased significantly ($P < 0.01$) compared with baseline when no local infiltration was used, but there was no significant change from baseline when infiltration with local anaesthetic preceded cannulation. We conclude that there is a significant pressor response to venous cannulation which is obtunded by prior infiltration with local anaesthetic. We recommend, therefore, that s.c. injection of lignocaine should be considered before insertion of an i.v. cannula, especially in the high risk patient. (Br. J. Anaesth. 1993; **70**: 519–521)

KEY WORDS

Anaesthetics, local: lignocaine. Complications: cardiovascular responses. Veins: cannulation.

Rate–pressure product (RPP) and mean arterial pressure (MAP) are important to the anaesthetist as accepted indicators of myocardial oxygen consumption [1] and intracranial pressure [2]. There has been a considerable amount of work performed attempting to minimize the increases in these variables associated with laryngoscopy and tracheal intubation [3]. These changes are especially important in high risk groups such as those with hypertension or increased intracranial pressure.

There have been no previous investigations on the effect of venous cannulation on RPP and MAP. Work in this department [4, 5] has already shown that the majority of anaesthetists do not use local anaesthetic before venous cannulation with small venous cannulae (18–22 gauge). We have shown also that patients find venous cannulation unpleasant and we could therefore formulate the hypothesis that venous cannulation would affect RPP and MAP. This study was undertaken to assess if such a response existed and if it could be attenuated by prior local anaesthetic infiltration.

PATIENTS AND METHODS

The study was approved by the Local Ethics Committee and written informed consent was obtained from all participants. We studied 40 adult patients undergoing minor elective surgical procedures under regional or general anaesthesia. Each patient was allocated randomly to one of two groups: group 1—venous cannulation with an 18-gauge Venflon; group 2—s.c. injection of 1% lignocaine 0.25 ml via a 25-gauge needle followed 1 min later by cannulation with an 18-gauge Venflon. Random allocation such that 20 patients entered each group was achieved by taking a pre-written card, blindly from a bag.

All patients were premedicated with temazepam 20 mg orally 1 h before surgery.

On arrival of the patient in the anaesthetic room, a Finapres non-invasive arterial pressure monitor (Ohmeda 2300) was placed on the middle finger of the patient's dominant hand. After a 5-min stabilization period, baseline recordings of heart rate, systolic pressure, diastolic pressure and MAP were obtained.

Cannulation or subcutaneous injection of local anaesthetic was then carried out by Investigator 1. The Finapres monitor and second investigator were separated from the patient and Investigator 1 by a screen. Readings were taken from the Finapres monitor by Investigator 2, who was unaware of the patient's group. Immediately upon cannulation or insertion of local anaesthetic, Investigator 1 informed the blinded Investigator 2 of time zero. Cardiovascular variables were recorded by Investigator 2 at times 0, 30 s, 1 min, 2 min and 3 min. In group 2, the local anaesthetic injection at time 0 was followed by cannulation 1 min later; Investigator 2 was unaware of this being performed. All cannulations were successful at the first attempt.

The baseline value for RPP was calculated for all patients, and the changes in RPP and MAP from the baseline at all subsequent time intervals were calculated. The results were analysed using Student's paired t test, Student's unpaired t test, Wilcoxon signed rank test, Mann–Whitney U test, analysis of variance or Kruskal–Wallis test where appropriate.

B. T. LANGHAM*, M.B., CH.B., F.R.C.ANAES.; D. A. HARRISON†, M.B., CH.B., F.R.C.ANAES.; University of Nottingham, Nottingham City Hospital and Queens Medical Centre, Nottingham NG7 2UH. Accepted for Publication: November 25, 1992.
Present addresses:
*Department of Anaesthesia, Leicester Royal Infirmary, Leicester LE1 5WW.
†Department of Anaesthesia, Royal Hallamshire Hospital, Sheffield.

Statistical analysis was performed using SPSS/PC+4.0 on an Elonex 386S PC with DR DOS 6.0.

RESULTS

Forty patients were studied (14 male), aged 18–70 yr (mean 40 yr); age and gender were matched equally in the two groups. There were no significant differences between the groups in baseline readings of systolic pressure, diastolic pressure, mean arterial pressure or heart rate (table I).

The mean changes in MAP and RPP from baseline values are shown in figures 1 and 2. The changes in MAP from the baseline value at each time interval were analysed using Student's paired *t* test, and changes in RPP by the Wilcoxon signed rank test. In group 2 (local anaesthetic infiltration before cannulation), there was no significant difference from baseline for either MAP or RPP, either at the time of infiltration or subsequently on cannula insertion. In group 1 (cannulation alone), significant increases in MAP ($P < 0.01$) and in RPP ($P < 0.01$) occurred after cannulation. These increases were sustained for the following 3 min.

TABLE I. *Mean* (SD) *cardiovascular responses to cannulation in patients without (group 1) or with (group 2) prior s.c. injection of 1 % lignocaine 0.25 ml. MAP = Mean arterial pressure; RPP = rate–pressure product; HR = heart rate*

	MAP (mm Hg)	HR (beat min^{-1})	RPP (mm Hg beat min^{-1})
Group 1			
Baseline	100.5 (18.5)	74.4 (11.7)	10602.1 (2515.3)
Time 0	108.1 (18.5)	80.0 (12.0)	12636.2 (3655.7)
30 s	106.8 (18.1)	77.6 (12.5)	12021.5 (3590.5)
1 min	108.3 (19.7)	75.2 (12.3)	11567.0 (2909.6)
2 min	109.2 (18.5)	74.4 (10.9)	11728.3 (3178.2)
3 min	106.5 (16.9)	75.0 (12.8)	11673.6 (3816.7)
Group 2			
Baseline	107.2 (22.0)	82.4 (14.6)	12164.7 (2204.1)
Time 0	107.0 (23.8)	81.1 (14.6)	12031.5 (2582.7)
30 s	106.6 (22.5)	76.4 (13.3)	11335.2 (2651.4)
1 min	106.9 (22.0)	78.0 (13.8)	11685.7 (2657.6)
2 min	107.1 (24.2)	77.3 (12.9)	11547.3 (2913.5)
3 min	107.1 (24.0)	77.6 (13.0)	11589.8 (3051.3)

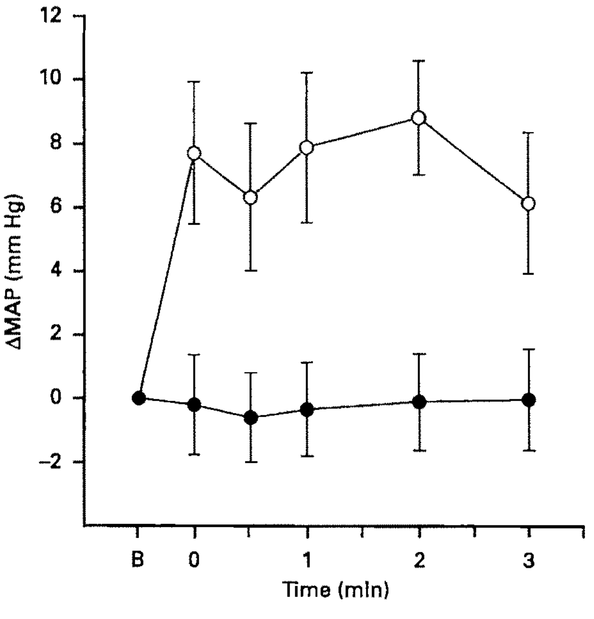


FIG. 1. Change in MAP from baseline (B) against time (mean, SEM). ○ = Group 1 (cannulation alone); ● = group 2 (s.c. injection of local anaesthetic followed at 1 min by cannulation). Time 0 = cannulation (group 1) or injection of local anaesthetic (group 2); time 1 min = cannulation in group 2.

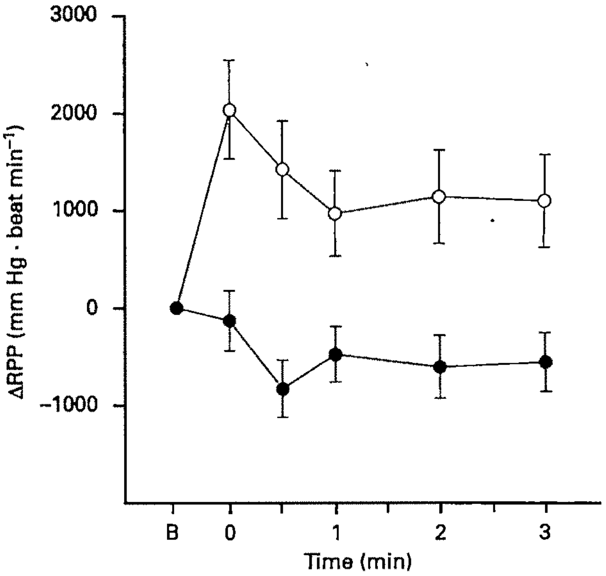


FIG. 2. Change in RPP from baseline (B) against time (mean, SEM). ○ = Group 1 (cannulation alone); ● = group 2 (s.c. injection of local anaesthetic followed after 1 min by cannulation). Time 0 = cannulation (group 1) or injection of local anaesthetic (group 2); time 1 min = cannulation in group 2.

The differences between groups in respect of MAP (Student's unpaired *t* test) and RPP (Mann–Whitney *U* test) were significant ($P < 0.01$) at each time during the study. Analysis of variance and the Kruskal–Wallis one-way ANOVA confirmed the effect of s.c. infiltration with lignocaine.

DISCUSSION

The Finapres is a non-invasive means of monitoring beat-to-beat variation in arterial pressure by means of a small inflatable finger cuff. The pressure in the cuff mimics digital artery pressure using a photoplethysmograph to determine flow cessation. It has been shown that the Finapres does not provide accurate between-patient measurements [6]; however, variability for within-patient measurements is acceptable. The Finapres is known to vary in its readings of MAP by as much as 20 mm Hg for up to 5 % of the time [7]. The MAP changes in our study group 1 were of the order of 10–15 mm Hg from baseline values; however, this change was sustained over a period of 3 min and did not occur in group 2. We conclude that the change observed in group 1 represents a true pressor response and cannot be attributed to inaccuracy of the Finapres.

We had shown previously [4, 5] that venous cannulation was unpleasant and painful and that these sensations were abolished by prior s.c. injection of local anaesthetic. The infiltration with local anaesthetic was found to be associated with minimal discomfort (median pain score of 1). From this work, we deduced that venous cannulation might affect RPP and MAP adversely and this has been confirmed by the results of the present study. We have shown also that the response to venous cannulation is abolished by the prior use of local anaesthetic infiltration, which suggests that the pressor response is not anticipatory in nature, but a reaction to the pain of cannulation.

Previous work has shown that changes in heart rate and the product of heart rate and systolic arterial pressure (RPP) reflect parallel changes in myocardial blood flow and myocardial oxygen consumption [8]. Gobel and colleagues [9] showed that RPP is the index which best correlates with myocardial oxygen consumption, and is therefore the critical one in defining the response of the coronary circulation to myocardial metabolic demand.

There is a large volume of published research on the pressor response to laryngoscopy and tracheal intubation during anaesthesia as these manoeuvres constitute a period of intense stimulation to the patient. The cardiovascular response may have adverse effects in patients with previously compromised coronary or cerebral circulation, and even healthy patients may suffer depression of left ventricular ejection fraction [10]. Many attempts have been made to obtund this response in high-risk patients using different agents and techniques, although no technique is associated with absolute cardiovascular stability. We have found a significant and sustained pressor response to venous cannulation in normotensive patients with a 10–15% increase in both MAP and RPP for at least 3 min. It would seem reasonable to expect there to be a proportionately greater response to this procedure in the hypertensive patient.

We conclude that s.c. local anaesthetic infiltration before venous cannulation should be a requirement in all patients, especially those deemed high risk, to maintain cardiovascular stability before other procedures are carried out.

REFERENCES

1. Barash PG, Kay H, Tinker J, Geha AS. Rate pressure product: A reliable index of myocardial oxygen consumption? *Anesthesiology* 1981; **55**: 37A.
2. Giffin JP, Cottrell LE, Shwiry B, Hartung J, Epstein J, Kongseh L. Intracranial pressure, mean arterial pressure and heart rate following midazolam or thiopental in humans with brain tumours. *Anesthesiology* 1984; **60**: 491–494.
3. Millar Forbes A, Dally FG. Acute hypertension during induction of anaesthesia and endotracheal intubation in normotensive man. *British Journal of Anaesthesia* 1970; **48**: 618–624.
4. Harrison N, Langham BT, Bogod DG. Appropriate use of local anaesthetic for venous cannulation. *Anaesthesia* 1992; **47**: 210–212.
5. Langham BT, Harrison DA. Local anaesthetic: does it really reduce the pain of insertion of all sizes of venous cannula? *Anaesthesia* 1992; **47**: 890–891.
6. Farquhar IK. Continuous direct and indirect blood pressure measurement (Finapres) in the critically ill. *Anaesthesia* 1991; **46**: 1050–1055.
7. Gibbs NM, Larach DR, Derr JA. The accuracy of Finapres noninvasive mean arterial pressure measurements in anesthetized patients. *Anesthesiology* 1991; **74**: 647–652.
8. Nelson RR, Gobel FL, Jorgensen CR, Wang K, Wang Y, Taylor HL. Hemodynamic predictors of myocardial oxygen consumption during static and dynamic exercise. *Circulation* 1974; **50**: 1179–1189.
9. Gobel FL, Nordstrom LA, Nelson RR, Jorgenson CR, Wang Y. The Rate Pressure Product as an index of myocardial oxygen consumption during exercise in patients with angina pectoris. *Circulation* 1978; **57**: 549–556.
10. Chraemmer-Jorgensen B, Hoilund-Carlsen PF, Marving J, Christensen V. Left ventricular ejection fraction during anaesthetic induction: comparison of rapid sequence and elective induction. *Canadian Anaesthetists Society Journal* 1986; **33**: 754–759.

British Journal of Anaesthesia 1993; **70**: 522–526

SURFACTANT AND ADULT RESPIRATORY DISTRESS SYNDROME

W. JACOBSON, G. R. PARK, T. SAICH AND J. HOLCROFT

SUMMARY

In order to determine if the Adult Respiratory Distress Syndrome (ARDS) is associated with a shortage of pulmonary surfactant, we have examined a series of 155 undiluted tracheal aspirates obtained from 23 patients with ARDS and from 30 patients without ARDS, all 53 needing ventilatory support. The unfixed and unstained specimens were examined by polarized light microscopy for the presence of pulmonary surfactant. Free surfactant particles were present in the aspirates of 50 patients (95%). Within minutes of obtaining the specimen, in addition to showing surfactant, the examination of these undiluted, unfixed tracheal aspirates by light microscopy showed the presence of bacterial and fungal infection. As fibrinogen/fibrin inactivates surfactant, the undiluted aspirates of 21 patients with ARDS and of 30 patients without ARDS were stained for the presence of these proteins by a new slide method using 0.01 ml of tracheal aspirate. Fibrinogen/fibrin was found in the aspirates from 20 of 21 patients with ARDS and in only five of 30 patients without ARDS; these five had bronchopneumonia. The method has a sensitivity of 0.95 and a specificity of 0.83. The role of plasma proteins and of neutrophil leucocytes in causing ARDS is discussed. (Br. J. Anaesth. 1993; **70**: 522–526)

KEY WORDS

Lung: adult respiratory distress syndrome, surfactant.

It is still uncertain if the Adult Respiratory Distress Syndrome (ARDS) is caused by failure to make adequate amounts of pulmonary surfactant or if this substance is made in near normal amounts, but is inactivated by plasma proteins that have leaked into the alveolar lumina.

The purpose of this study was to establish the presence or absence of specific surfactant particles in undiluted tracheal aspirates of patients whose trachea was intubated, who needed ventilatory support and who either developed or had ARDS, in contrast with those who did not develop this complication. If there was no significant difference in the finding of surfactant particles between these two groups, this would lend support to the inactivation mechanisms. Fibrinogen/fibrin is known to inactivate pulmonary surfactant [1, 2].

Microscopic examination of undiluted, unstained tracheal aspirates in polarized light reveals the presence of the characteristic surfactant particles; examination in ordinary light may reveal the presence of large numbers of bacteria and fungi, thus showing the onset or presence of infection.

MATERIALS AND METHODS

Specimens of tracheal aspirate were obtained by inserting a sterile catheter approximately 3–4 cm beyond the end of the tracheal tube. No water or saline was used for this procedure, allowing undiluted secretions from the lower end of the trachea to be obtained. The aspirates were collected into a sputum trap (Bard, Crawley, U.K.) placed in a refrigerator at 3 °C to await transfer to the laboratory. This usually took less than 1 h. Specimens stored in this way have no changes in surfactant, cellular details or other features for at least 48 h. Specimens for microscopic examination were prepared by taking a sample of the aspirate from the sputum trap with a sterile loop, and placing it onto a microscope slide. No more than 10 µl was used. The specimen was covered immediately with a coverslip (22 × 22 mm, thickness grade 0), without any pressure. In order to prevent evaporation, the slides were stored at 3 °C in a small plastic box containing a strip of moist filter paper. Under these conditions, the slides could be re-examined 3 days later without significant changes having occurred in cells or surfactant particles, except that some spherical surfactant particles had undergone hydration and appeared now as ring-shaped liposomes.

Nearly all tracheal aspirates were examined by two observers (W.J. and T.S.) who were unaware of the clinical state of the patients. There was good agreement between the two observers—only three specimens needed re-assessment. A total of 155 tracheal aspirates from 53 unselected adult patients (ages 17–85 yr (median 62 yr); 28 male) was available. Table I shows the diagnoses on admission to the Intensive Care Unit and the patients who did or did not develop ARDS. There were 30 patients (17 male) who did not have ARDS and 23 (11 male) who had ARDS.

The clinical diagnosis of ARDS was made using the definition of Maunder and Hudson [3], based on

---

W. JACOBSON, M.D., PH.D., SC.D., F.R.C.P., F.R.C.PATH., T. SAICH (University Department of Paediatrics); G. R. PARK, M.D., F.R.C.ANAES., J. HOLCROFT, S.R.N. (Department of Anaesthesia); Addenbrooke's Hospital, Cambridge CB2 2QQ. Accepted for Publication: December 8, 1992.

Correspondence to W.J.

TABLE I. *Diagnosis of patients on admission to the Intensive Care Unit who developed ARDS and who did not.* **Excluding malignancy*

	ARDS	Non-ARDS
Liver transplant	6	6
Pneumonia	5	5
Multiple trauma	5	4
Malignancy	0	5
Aortic aneurysm	2	1
Myocardial infarct	0	3
Vasculitis	1	1
Oesophageal pathology*	2	0
Intestinal pathology*	1	1
Pancreatitis	1	1
Renal pathology	0	1
Guillain Barré	0	1
Chronic obstructive airways disease	0	1
Total	23	30

their previous paper [4]. The following five conditions were required for the diagnosis of ARDS: presence of respiratory distress, hypoxaemia, an increase in $F\mathrm{I}_{\mathrm{O}_2}$ failing to alleviate respiratory distress, generalized infiltrations of chest radiographs and exclusion of other cardiovascular or respiratory diseases.

Microscopic examination

Polarized light. The specimens were examined at a magnification of ×400 using a strong light source. Surfactant particles are birefringent and appear as bright spherical granules 0.5–3 μm in diameter, with a cross of polarization, against a black background. Most of the particles lie free in the secretion, but some may have been taken up by macrophages. It should be noted that the distribution of surfactant particles is usually uneven, as frequently they are in strands of secretion. Stable air bubbles, strongly birefringent (therefore lined by surfactant and remaining unchanged for 24 h), with a diameter ranging from less than 1 μm to about 30 μm, are also an indication of the presence of this substance.

Light microscopy. The unstained, wet preparation was examined with a narrow iris at magnifications of ×125 and ×400 to show cellular elements, micro-organisms (including fungal hyphae), haemosiderin (yellow brown), bile pigments (appearing as golden or green particles 1–3 μm in diameter) and aspirated matter, similar to milk fat droplets, refractile but not birefringent. For photographic records, phase contrast and darkfield illumination were used.

Stained specimens. Samples from all aspirates were spread on microscope slides. One slide was stained with Leishman's dye to make a permanent preparation of the cellular components and a second slide was stained with Grams's method, to record the presence of micro-organisms.

As ARDS is associated with increased permeability of capillary endothelial cells, staining procedures were developed for the presence of some plasma proteins in the tracheal aspirates. For this purpose, a droplet of secretion (not more than 10 μl) was spread on a slide over an area of 2 cm diameter. After drying in air, it was fixed immediately in 100% methanol for 2 min at room temperature, and dried in air again. The slides were then stained for fibrinogen/fibrin, immunoglobulin A (IgA) and albumin.

The fixed, air-dried specimen was placed in a Coplin jar with anti-human fibrinogen, developed in goat (Sigma F2.506), at a dilution of 1:1000 with tris saline buffer 0.05 mol litre^{-1} at pH 8.2 at 3 °C for 18 h. It was then washed twice, for 5 min in the buffer. The slide was then transferred to another Coplin jar containing anti-goat immunoglobulin (developed in rabbit)–alkaline phosphatase conjugate (adsorbed with human serum proteins, Sigma A4049) at a dilution of 1:1000 with tris saline buffer 0.05 mol litre^{-1} (pH 8.2) at 3 °C for 18 h. After two washes of 5 min in the buffer, the slide was placed in a freshly prepared solution of napthol AS/MX phosphate 2 mg, N, N- dimethylformamide 0.2 ml, tris saline buffer 0.05 mol litre^{-1} (pH 8.2) 9.8 ml, 20 μl of levamisole 1 mol litre^{-1}, Fast red TR salt 10 mg and 50 μl of magnesium chloride 1 mol litre^{-1}, and stained for 30 min at room temperature. (All chemicals from Sigma Chemical Company Ltd, Poole, Dorset, U.K.) The staining solution was filtered through Whatman No. 1 paper before use. The preparation was counterstained with 0.2% methyl green for 5 min, washed in running tap water for 5 min, then air-dried and mounted in DPX (BDH/Merck, Slaughter Ltd, Upminister, Essex U.K.).

A total of 120 slides was prepared by this method. The presence of fibrinogen/fibrin is shown in bright red colour. About 25 μg of fibrinogen/fibrin in 10 mg of wet aspirate appears bright red to the naked eye. Traces of fibrinogen/fibrin about 1 μg in the same volume appear as small red clumps or streaks under ×100 magnification, but in the absence of fibrinogen/fibrin the slides remain colourless. The optional counterstain with methyl green shows cell nuclei and glycoproteins of mucus in bright green colour. Staining for immunoglobulin A and albumin was with the corresponding antisera on separate slides.

The presence of surfactant in the tracheal aspirates was classified:

Abundant = most fields at ×400 magnification contained characteristic free surfactant particles.

Adequate = free particles were found in some, but not in other fields.

Few = an extensive search was required to detect any free particles.

None.

The presence of macrophages with ingested surplus surfactant particles was always considered an indication of adequate surfactant. The presence of strongly birefringent, stable air bubbles, even in the absence of free surfactant particles, was also taken as showing adequate surfactant. Owing to the uneven distribution of surfactant particles that were often entrapped in strands of mucus, more exact quantition was not feasible.

RESULTS

There was no difference in the occurrence of free surfactant particles in the tracheal aspirates of the 30 patients without ARDS and the 23 patients with

TABLE II. *Surfactant particles (and strongly birefringent air bubbles) in tracheal aspirates of patients (No. (%)) with and without ARDS. (For definition of terms see Materials and Methods)*

Surfactant particles	ARDS group ($n = 23$)	Non-ARDS group ($n = 30$)
Abundant	8 (35)	9 (30)
Adequate	12 (52)	16 (53)
Few	1 (4)	4 (13)
Only birefringent stable air bubbles	2 (9)	1 (3)
Total	23	30

ARDS (table II). This statement is based on the findings in 67 and 88 aspirates from these two groups, respectively. Chi-square analysis showed that for d.f. = 3, $P = 0.6$, thus confirming that there is no significant difference in the findings of free surfactant particles in the aspirates of patients with and without ARDS. In both groups, macrophages with ingested birefringent surfactant particles (with a cross of polarization) were a frequent finding.

The presence of fibrinogen/fibrin in the tracheal aspirates was strikingly different between the two groups. Whereas 25 of 30 patients without ARDS had no traces of these proteins in their 46 aspirates, 20 of 21 patients with ARDS did have these proteins present. The five patients without ARDS and with more than traces of fibrinogen/fibrin in their samples (four of them were weakly positive) had clinical and radiological evidence of bronchopneumonia. These five patients (of 30) must be considered "false" positive. There was one patient in the ARDS group of 21 whose four samples of tracheal aspirate showed only traces of fibrinogen/fibrin. He must be counted as a "false" negative. Thus the test for fibrinogen/fibrin to distinguish between ARDS and non-ARDS patients has a sensitivity of $20/21 = 0.95$, a specificity of $25/30 = 0.83$, with a predictive value of $45/51 = 0.88$.

Of the 21 patients with ARDS 14 (38 aspirates) stained positive for fibrinogen/fibrin in their first sample. Of these 14 patients, five were followed up until they recovered, when their aspirate became free from fibrinogen/fibrin. Another group of six patients whose 25 samples were negative at first when they did not have ARDS, subsequently tested positive when they developed the disease. Of this group of six patients, three were followed up until they recovered from ARDS, when their tracheal aspirates were free even from traces of fibrinogen/fibrin.

A large number of bacteria, together with numerous leucocytes, were found in the aspirates of 10 of the 30 patients without ARDS and in 11 of the 23 patients with ARDS, indicating infection. The presence of an occasional micro-organism was not considered to be clinically significant. Candida pseudohyphae surrounded by numerous leucocytes were seen in the aspirates of two patients without ARDS and in six patients with ARDS. The aspirate of one patient with ARDS contained aspergillus hyphae among numerous leucocytes. The presence of the occasional small group of candida or a single pseudohypha was not considered to be a sign of a fungal infection. It should also be noted that the presence of numerous neutrophil leucocytes without bacteria/hyphae in an aspirate is no indication of an infection.

DISCUSSION

This study of undiluted tracheal aspirates in polarized light is the easiest, quickest and cheapest method of establishing the presence of surfactant. Only a small amount of aspirate (not more than 0.01 ml) is needed. This simple technique allowed every aspirate to be evaluated for the presence of surfactant particles, however much contaminated by pus or blood, as the surfactant particles show up brightly against a dark background. Such contaminations render specimens unsuitable for biochemical analysis or surface tension measurements, which are the usual methods of measuring surfactant. The surfactant particles always remained separated, never agglutinated.

The two main findings of this investigation are the similar occurrence of free surfactant particles in the tracheal aspirates of 30 patients without ARDS and 23 with ARDS and the presence of fibrinogen/fibrin in the aspirates of only five of 30 patients without, but in 20 of 21 patients with ARDS.

In order to relate these two types of observations to the cause of ARDS, it has to be established that the 0.5–3 μm round, birefringent particles with a cross of polarization are surfactant particles. They are identical to those found in the type II cells of alveolar epithelium, the particles found in the lumen of the alveoli, in the tracheal aspirates of neonates and in the amniotic fluid after the 20th week of gestation. They have a large content of phosphatidylcholine and palmitate and can decrease surface tension to 10 mN m^{-1}. They are rare in the amniotic fluid of infants born with RDS and in the lungs of infants who died with RDS during the first 2 days after birth. Thus there is sufficient evidence that the characteristic particles represent an important form of surfactant [5–7]. It should be remembered that the surfactant particles in the aspirates were secreted into alveoli already coated with surfactant, thus representing surplus surfactant.

The presence of similar amounts of surfactant particles in 88 tracheal aspirates of 23 patients with ARDS and in 67 aspirates of 30 patients without the disease make it unlikely that ARDS is caused primarily by a shortage of pulmonary surfactant. In view of the known capacity of fibrinogen/fibrin to inactivate surfactant [1, 2], and described by Ashbaugh and his colleagues [8] in ARDS, it is most likely that these proteins have interfered with the function of surfactant, as they were found in 20 of 21 patients with ARDS and only in five of 30 patients without ARDS, all five having bronchopneumonia. The appearance of fibrinogen/fibrin in the aspirates correlated with the onset of ARDS in the six patients in whom aspirates were available before they developed ARDS. Conversely, these proteins disappeared from the tracheal aspirates in the eight patients who recovered from ARDS.

The inactivation of pulmonary surfactant by fibrinogen/fibrin and other plasma proteins has been

TABLE III. *Phospholipid values per ml of lavage fluid as reported by Pison and colleagues [7] and as calculated from the data of Gregory and colleagues [6] (see Appendix).* n = *No. samples*

	Phospholipid (μg ml^{-1})	
	Gregory	Pison
Normal	15.0 ($n = 29$)	84.1 ($n = 29$)
"At risk" or low score ARDS	11.0 ($n = 20$)	65.7 ($n = 77$)
ARDS	5.4 ($n = 66$)	65.1 ($n = 58$)

studied extensively [1, 2, 8–14]. A faulty synthesis of the surfactant lipid as a cause of ARDS has not been detected. The physical subtypes of surfactant are not caused by a change in lipid synthesis [15].

The question if inactivation of surfactant by plasma proteins, inadequate synthesis of it, or both, causes ARDS has been examined by two groups who came to opposite conclusions: Gregory and colleagues [16] found a 45 % reduction in phospholipids in lavage fluid of patients with ARDS compared with an "at risk" group and also a reduction by 67 % compared with the lavage fluid of normal persons. Conversely, Pison and colleagues [17] found no difference in the content of the lavage fluid of ARDS and non-ARDS patients. Gregory's group reported their findings as µmol of phospholipid in the reconstituted high-speed pellet of the lavage fluid, while Pison's group reported their findings as phospholipid µg/ml lavage fluid. In order to compare their respective findings, the former values must be converted to the latter. The calculations are given in the Appendix. Table III shows Pison's much greater values of phospholipid extracted from lavage fluid of the three groups (normal, non-ARDS and ARDS patients) and that there is no difference in the amount of phospholipid found in the lavage fluid of the two groups of patients. Our own observations on tracheal aspirates (not lavage fluid), using polarized light microscopy, are in agreement with those of Pison's group.

The problem of inactivation of pulmonary surfactant is a complex one, as other plasma proteins such as albumin and IgA can interfere with its function. Furthermore, the surfactant proteins SP-A, SP-B and SP-C can protect the lipid from inactivation by plasma proteins [18–23].

The leakage of plasma proteins into the alveoli is caused by damage of the alveolar endothelial cells. One of the factors contributing to this damage is that activated neutrophils stick to the endothelium and emigrate into the air spaces. They produce toxic oxygen radicals [24–32] which can also affect the endothelium [33, 34]. Although artificial surfactant may bring temporary relief [35], it does not prevent the capillary damage. Prevention of capillary damage by means of specific inhibitors of enzymes in neutrophils, which produce toxic oxygen radicals that in turn damage the blood–air barrier, would be a promising target for therapeutic research.

The presence of large numbers of white blood cells (WBC) in the aspirates, mainly neutrophils and macrophages/monocytes, is no indication of an infection [36]; damaged lung parenchyma may have induced the emigration of WBC. A clinically important infection was diagnosed only when the aspirate contained numerous micro-organisms with numerous WBC (except in a leukopenic patient). The high incidence of infections among the ARDS patients (78 %) compared to the non-ARDS group (43 %) is in agreement with others [37].

It is likely that inactivation of surfactant by plasma proteins is important in the development of ARDS. However, later in the disease process, when hyaline membranes coat increasing areas—indicating loss of epithelial cells in the alveoli and respiratory bronchioles—production of surfactant may be reduced.

APPENDIX

To convert the values of Gregory and colleagues [16] of phospholipid µmol/ml reconstituted high speed pellet into phospholipid µg/ml lavage fluid as reported by Pison and colleagues [17] (see table III):

(1) Gregory's group used saline 3 × 50 ml for lavage; Pison's group used saline 5 × 20 ml.

(2) Recovery of lavage fluid by Gregory's group for normal control was 95 ml, for "at risk" patients 56 ml, for ARDS patients 83 ml. Pison's group recovered 60–70 ml for all three groups.

(3) Gregory's group reconstituted the high speed pellet for measurement of phospholipid with 0.2 ml saline. As they report the amount of phospholipid in µmol/ml reconstituted pellet, their figures must be divided by 5 to obtain the actual amount of phospholipid extracted from the high speed pellet.

Normal group. Phospholipid 7.99 µmol/ml reconstituted pellet divided by 5 = phospholipid 1.6 µmol in 85 ml of lavage fluid (from 95 ml recovered, some was taken for cell counts, cytology and bacteriology); thus phospholipid 0.019 µmol/ml lavage fluid. To convert phospholipid µmol into µg, multiply by 775, assuming an average molecular weight of various phospholipids as 775 (some authors assume 750; we chose the greater value to give advantage to Gregory's group). Thus 1 ml of lavage fluid of normal subjects contained phospholipid 15 µg/ml lavage fluid.

"At risk group". Phospholipid 3.38 µmol/ml reconstituted pellet converts to phospholipid 11 µg/ml lavage fluid (assuming a 50-ml volume of phospholipid PL). They recovered 56 ml minus deductions (see above).

ARDS group. Phospholipid 2.47 µmol/ml reconstituted pellet converts to phospholipid 5 µg/ml lavage fluid (assuming a 75-ml volume, they recovered 83 ml minus deductions).

(Summarized in table III.)

ACKNOWLEDGEMENT

The generous support by the Trustees of the Sir Halley Stewart Trust is gratefully acknowledged. W. J. is the Sir Halley Stewart Professor of Medical Research.

REFERENCES

1. Abrams ME, Taylor FB. Isolation and quantitive estimation of pulmonary surface active lipoprotein and its interaction with fibrinogen. *Physiologist* 1964; 7: 78.
2. Taylor FB, Abrams ME. Effect of surface active lipoprotein on clotting and fibrinolysis, and of fibrinogen on surface tension active lipoprotein. *American Journal of Medicine* 1966; 40: 346–350.
3. Maunder RJ, Hudson LD. Clinical risks associated with Adult Respiratory Distress Syndrome. In: Zapol WM, Lemaire F, eds. *Adult Respiratory Distress Syndrome*, chapter 1. New York: Dekker Inc., 1991; 1–21.
4. Maunder RJ, Hudson LD. The Adult Respiratory Distress Syndrome. In: Simmon DH, ed. *Current Pulmonology*, Vol. 7. Chicago: Year Book Medical Publishers, 1986; 97–116.
5. Gandy G, Jacobson W, Gairdner D. Hyaline Membrane Disease 1. cellular changes. *Archives of Disease in Childhood* 1970; 45: 289–310.
6. Jacobson W, South M, Hughes G, Davies R, Morley C.

Tracheal aspirates from neonates during endotracheal intubation. Detection of surfactant by polarised light microscopy. *Journal of Pediatrics* 1988; **113**: 368–372.
7. Clark HW, Jacobson W. Polarised light microscopy of amniotic fluid: a rapid method to assess fetal lung maturity—a pilot study. *Journal of Obstetrics and Gynaecology* 1991; **11**: 307–314.
8. Ashbaugh DG, Bigelow DB, Petty TL, Levine BE. Acute respiratory distress in adults. *Lancet* 1967; **2**: 319–323.
9. Henry JN. The effect of shock on pulmonary alveolar surfactant. Its role in refractory respiratory insufficiency of the critically ill or severely injured patient. *Journal of Trauma* 1968; **8**: 756–773
10. Petty TL, Reiss OK, Paul GW, Elkins ND. Characteristics of pulmonary surfactant in Adult Respiratory Distress Syndrome associated with trauma and shock. *American Review of Respiratory Disease* 1977; **115**: 531–536.
11. Hallman M, Spragg R, Harrell JH, Moser KM, Gluck L. Evidence of lung surfactant abnormality in respiratory failure. Study of bronchoalveolar lavage phospholipids, surface activity, phospholipase activity and plasma myoinositol. *Journal of Clinical Investigation* 1982; **70**: 673–683.
12. Ikegami M, Jobe A, Berry D. A protein that inhibits surfactant in Respiratory Distress Syndrome. *Biology of the Neonate* 1986; **50**: 121–129.
13. O'Brodovich HM, Weitz JI, Possmayer F. Effect of fibrinogen degradation products and lung ground substance on surfactant function. *Biology of the Neonate* 1990; **57**: 325–333.
14. Kobayashi T, Nitta K, Ganzuka M, Inui S, Grossman G, Robertson B. Inactivation of exogenous surfactant by pulmonary oedema fluid. *Pediatric Research* 1991; **29**: 353–356.
15. Higuchi R, Lewis J, Ikegami M. *In vitro* conversion of surfactant subtypes is altered in alveolar surfactant isolated from injured lungs. *American Review of Respiratory Disease* 1992; **145**: 1416–1420.
16. Gregory TJ, Longmore WJ, Moxley MA, Whitsett JA, Reed CR, Alpha A, Fowler M, Hudson LD, Maunder RJ, Crim C, Hyers TM. Surfactant chemical composition and biophysical activity in Acute Respiratory Distress Syndrome. *Journal of Clinical Investigation* 1991; **88**: 1976–1981.
17. Pison U, Seeger W, Buchhorn R, Joka T, Brand M, Obertake U, Neuhof H, Schmit-Neuerburg K-P. Surfactant abnormalities in patients with respiratory failure after multiple trauma. *American Review of Respiratory Disease* 1989; **40**: 1033–1039.
18. Holm BA, Venkitaraman AR, Enhorning G, Notter RH. Biophysical inhibition of synthetic lung surfactants. *Chemistry and Physics of Lipids* 1990; **52**: 243–250.
19. Cockshutt AM, Weitz J, Possmayer F. Pulmonary surfactant-associated protein A enhances the surface activity of lipid-extract surfactant and reverses inhibition by blood proteins *in vitro*. *Biochemistry* 1990; **29**: 8424–8429.
20. Idell S, Koenig KB, Fair DS, Martin TR, McLarty J, Maunder RJ. Serial abnormalities of fibrin turnover in evolving Adult Respiratory Distress Syndrome. *American Journal of Physiology* 1991; **261**: L240–248.
21. Venkitaraman AR, Hall SB, Whitsett JA, Notter RH. Enhancement of biophysical activity of lung surfactant extracts and phospholipid–apoprotein mixtures by surfactant protein A. *Chemistry and Physics of Lipids* 1990; **56**: 185–194.
22. Venkitaraman AR, Baatz JE, Whitsett JA, Hall SB, Notter RH. Biophysical inhibition of synthetic phospholipid lung surfactant apoprotein admixtures by plasma proteins. *Chemistry and Physics of Lipids* 1991; **57**: 49–57.
23. Hallman M, Merritt TA, Akino T, Bry K. Surfactant protein A, phosphatidylcholine, and surfactant inhibitors in epithelial lining fluid. *American Review of Respiratory Disease* 1991; **144**: 1376–1384.
24. Tagan M-C, Markert M, Schaller M-D, Feihl F, Chiolero R, Perrett CH. Oxidative metabolism of circulating granulocytes in Adult Respiratory Distress Syndrome. *American Journal of Medicine* 1991; **91** (Suppl. 3c): 72S–78S.
25. Doelman CJA, Bast A. Oxygen radicals in lung pathology. *Free Radicals in Biology and Medicine* 1990; **9**: 381–400.
26. Fisher MA, Malik AB. Interactions between neutrophils and endothelial cells mediate lung vascular injury. *Applied Cardiopulmonary Pathophysiology* 1991; **4**: 175–189.
27. Swank DW, Moore SB. Roles of the neutrophil and other mediators in Adult Respiratory Distress Syndrome. *Mayo Clinic Proceedings* 1989; **64**: 1118–1132.
28. McNee W, Selby C. Neutrophil kinetics in the lungs. *Clinical Science* 1990; **79**: 97–107.
29. van Asbeck BS. Involvement of oxygen radicals and blood cells in the pathogenesis of ARDS by endotoxin and hyperoxia. *Applied Cardiopulmonary Pathophysiology* 1991; **4**: 127–137.
30. Petty TL. Early treatment and recovery phase of ARDS. *Applied Cardiopulmonary Pathophysiology* 1989; **3**: 21–31.
31. Martin TR, Pistorese BP, Hudson LD, Maunder RJ. The function of lung and blood neutrophils in patients with the Adult Respiratory Distress Syndrome. *American Review of Respiratory Disease* 1991; **144**: 254–262.
32. Weiss SJ. Tissue destruction by neutrophils. *New England Journal of Medicine* 1989; **320**: 365–376.
33. Malik AB. Pulmonary microembolism and lung vascular injury. *European Respiratory Journal* 1990; **3** (Suppl. 11): 499S–506S.
34. MacNaughton PD, Evans TW. Management of Adult Respiratory Distress Syndrome. *Lancet* 1992; **339**: 469–472.
35. Morton NS. Exogenous surfactant treatment for the Adult Respiratory Distress Syndrome. A historical perspective. *Thorax* 1990; **45**: 825–830.
36. Menduri GL, Belenchia JM, Estes RJ, Wunderink RG, Torky M, Leeper KV. Fibroproliferative phase of ARDS. Clinical findings and effects of corticosteroids. *Chest* 1991; **100**: 943–952.
37. Zapol WM, Frikker MJ, Pontoppidan H, Wilson RS, Lynch KE. The Adult Respiratory Distress Syndrome at Massachusettes General Hospital. In: Zapol WM, Lemaire F, eds. *Adult Respiratory Distress Syndrome*, chapter 16. New York: Dekker Inc., 1991; 367–380.

British Journal of Anaesthesia 1993; **70**: 527–531

PENETRATION OF AN AEROSOL, PRODUCED BY FILM ATOMIZATION, THROUGH THE CARINAL BIFURCATION

T. J. J. INGLIS, J. G. JONES AND S. PAXTON

SUMMARY

We have measured the size of spots produced by atomization of simulated biofilm particles from a tracheal tube. Draughtsman's ink was atomized from 8.5-mm i.d. Portex tracheal tubes, using an airflow of 1 litre s^{-1}, and trapped on vertical acetate sheets. The spots produced by these particles were compared with the spot size after entrainment and dissemination from an ink-lined tracheal tube through a bifurcating tracheobronchial tube towards a glass plate. Spot dimensions were measured by computer-assisted image analysis of a video image. The smallest particles observed on the acetate sheets were 4–17 µm in size. In the bifurcating tube experiment, large particles were deposited around the carinal bifurcation, but smaller particles traversed the bend. The smallest spot size observed (7 µm minimum; 17 µm median) corresponds to particles small enough to penetrate further into the lower respiratory tract. Travel via a tube similar to the carinal bifurcation suggests that fragments of biofilm entrained in the tracheal tube could be propelled deeper into the respiratory tract during the inspiratory phase of mechanical ventilation. (Br. J. Anaesth. 1993; **70**: 527–531)

KEY WORDS

Airway: aerosol penetration. Equipment: tracheal tube.

Critically ill patients are at increased risk of nosocomial pneumonia. Although pneumonia in patients undergoing artificial ventilation is often attributed to bacteria from endogenous flora, the mechanism by which these organisms are finally disseminated into the lungs has not been defined. It has been suggested that the material lining the inner surface of the tracheal tube ("tracheal tube biofilm") can be dislodged and carried further into the lung during suction catheter movement [1]. More recently, it was shown that the gas–liquid interaction between airflow along the tracheal tube and biofilm lining the tube could dislodge bacteria from the biofilm and scatter this material over a range of many centimetres [2]. That study did not explore the likelihood of dissemination through a branched tube system such as the trachea and bronchi. In the present study, biofilm dissemination from the tracheal tube was simulated to determine the size of the smallest particles produced and to examine if they would traverse a Y junction constructed to the dimensions of the trachea and main bronchi.

MATERIALS AND METHODS

Atomization

Particle atomization produced by an interaction between gas flowing through a liquid lining the tracheal tube was studied in the following manner. A preweighed Portex tracheal tube of 8.5-mm i.d. was straightened and pointed horizontally towards a vertical acetate sheet held at 32 cm from the tip of the tube. A 1.0-ml bolus of draughtsman's ink (Rotring GmbH, Germany) was placed in the distal 3 cm of tube, and allowed to pool along the tube. A ventilator (Erica, Engstrom, Denmark) was connected to the tracheal tube connector using standard ventilator tubing and run for a single cycle to give a flow rate of 1 litre s^{-1} (i.e. a tidal volume of 1 litre in 1 s) measured with a Fleisch II pneumotachograph. The acetate sheet was removed immediately and air dried while held at room temperature in a horizontal position. This procedure was repeated nine times under identical conditions, using a fresh tracheal tube each time. After each experiment, the tube was sealed with paraffin film to contain the remaining liquid during transport and reweighed after removal of the film to calculate the mass of liquid entrained.

A further series of experiments was carried out when particles entrained from the tracheal tube were directed via a horizontal bifurcating tube towards a vertical sheet of 2-mm picture glass. The bifurcating tube used in the procedure was constructed to the dimensions of the trachea and main bronchi as described by Weibel [3]. The bifurcating tube was designed and constructed in the workshops of the Royal Aircraft Establishment, Farnborough, and had a constant cross sectional area between "tracheal" and "bronchial" levels. The Portex tracheal tube was held horizontally and placed in the "tracheal" part of the bifurcating tube, after which the cuff was inflated to seal the tube in the model trachea. The glass sheet was placed perpendicular to the direction of flow, 2.5 cm from the distal end of each bifurcation (the total distance between tracheal

---

TIMOTHY J. J. INGLIS*, D.M., M.R.C.PATH., D.T.M.&H. (Department of Microbiology); STEPHEN PAXTON (Department of Anatomy); University of Leeds, Leeds LS2 9JT. J. GARETH JONES, M.D., F.R.C.P., F.R.C.ANAES., Department of Anaesthesia, University of Cambridge, Addenbroke's Hospital, Cambridge CB2 2QQ. Accepted for Publication: December 3, 1992.

*Present address, for correspondence: Department of Microbiology, National University of Singapore, Lower Kent Ridge Road, Singapore 0511.

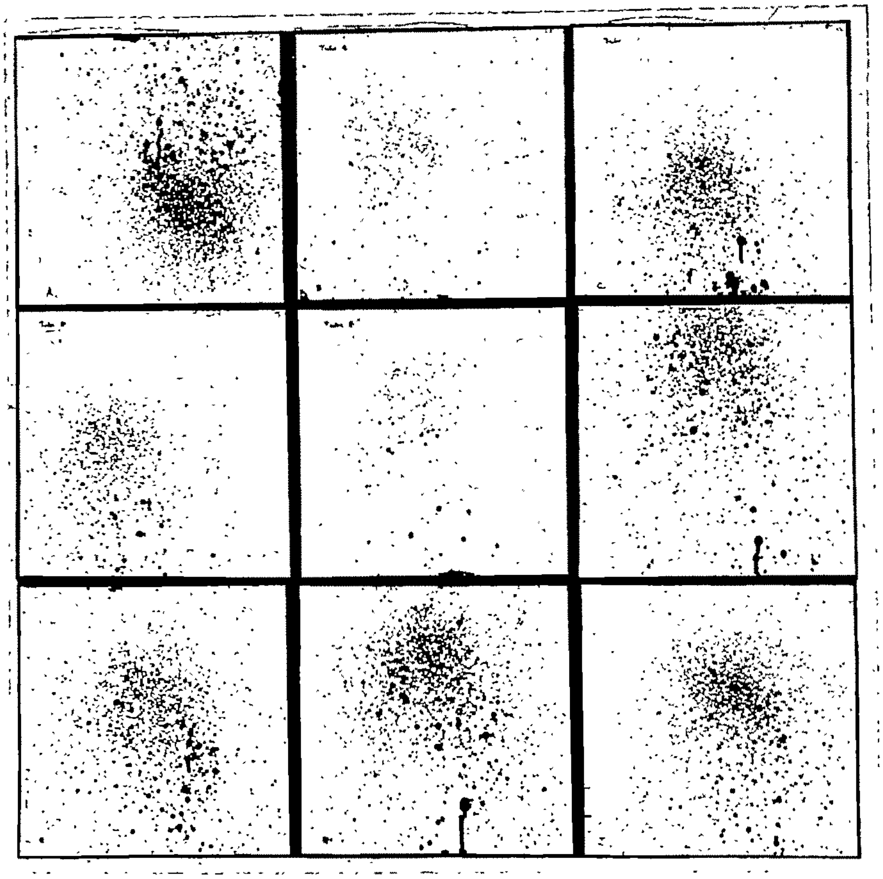


FIG. 1. Ink scatter produced at 32 cm from tips of adult tracheal tubes, replicated nine times. (For details of the particles, see table I.)

tube tip and glass being 32 cm), and inspiratory flow was simulated by running the ventilator for a single cycle. The same ink volume, loading technique, ventilator and cycle were used in this experiment as described above. The experiment was repeated without the intervening Y-piece, and a fresh glass sheet held at 32 cm from the tracheal tube tip.

Image analysis

The nine acetate sheets were examined initially by light microscope (magnification × 400, with graticule eyepiece) to obtain an estimate of the range of spot sizes. To avoid losing spot images as a result of buckling or detachment from the acetate sheets, the sheets were photographed with 35-mm black-and-white film. The negatives were then digitized using the CCTV camera and a dissecting microscope (Wild, Heerbrugg, Switzerland) and scanned in a single straight line from the area of most dense particle deposition at the centre of the scatter pattern to its furthest edge. The smallest spots were selected visually from the video screen and at least four possible spots were measured from each pattern. Total object number, total object area, mean object area and the *D* value (diameter of a circle of area identical to that of the scanned image of each spot) were obtained using the image analyser. Pixel dimensions were 0.6 × 1.1 μm. The software used was Vidi-pp version 1.0 (ULIS, Leeds) running under DOS 4.01 on an IBM-compatible microcomputer (Elonex PC 486B/25) with a framegrabber (ROMBO, Livingstone, Scotland), a CCTV monochrome camera (Hitachi, U.K.), and a photomicroscope (photomicroscope model II, Zeiss, Germany).

Glass sheets were used in the Y-tube procedure to avoid problems with buckling and loss of ink spots during microscopy. Glass was also used to reduce any electrostatic repulsion of smaller particles by the surface on which impaction would occur. Spots produced by particles passing through the bifurcating tube were deposited in a broad crescent-shaped area. A 2.5 × 2.5-mm square was chosen for image analysis in the wider part of the crescent, avoiding the larger spots, as these were large enough to obscure several smaller ones. This area was marked on the plate and subjected to image analysis, as above.

RESULTS

Extensive entrainment of liquid lining the tube resulted in extensive scatter of ink spots each time the experiment was repeated, although there was some variation in the quantity of material deposited on the acetate sheets (fig. 1, table I).

In the bifurcating airway experiment, most spots large enough to be seen easily with the naked eye were deposited on the Y-tube wall at the bifurcation (fig. 2). Nevertheless, a collection of smaller spots was obtained on the glass plates positioned opposite the "bronchial" branches of the Y-tube. Most of these particles could not be seen easily without magnification. When their distribution was com-

TABLE I. *Characteristics of ink particles produced in each of nine replicate scatter experiments depicted in figure 1*

Scatter pattern	Liquid entrained (g)	Minimum spot diam. (µm)	No. spots	Spot area (mm²) Total	Spot area (mm²) Mean
A	0.77	6.7	1188	27.6	0.023
B	0.41	13.3	435	3.6	0.008
C	0.73	4.1	986	15.3	0.016
D	0.85	4.8	947	11.4	0.012
E	0.58	17.2	201	3.4	0.017
F	0.78	6.5	1045	18.3	0.018
G	0.80	8.1	1355	20.4	0.015
H	0.79	8.4	1224	22.9	0.019
I	0.66	7.1	1537	23.2	0.015

pared with the scatter pattern obtained at the same distance without an intervening bifurcating tube, there was a readily visible difference between the spot size distribution on the respective plates (fig. 3). The minimum diameter of particles disseminated from the tracheal tube following flow through the Y-piece was 7 µm (mode was 17 µm) (fig. 4).

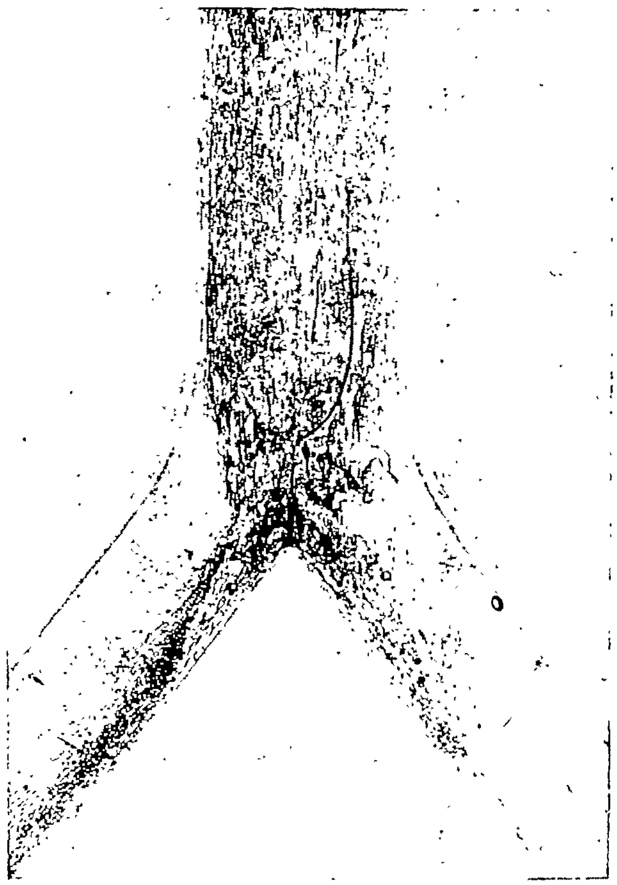


FIG. 2. Deposition of ink particles at the bifurcation of a Y-shaped tube.

DISCUSSION

Particle deposition in the lungs of spontaneously ventilating subjects has been investigated previously [4] and two-phase gas–liquid flow recognized as a mechanism for mucus transport in the airways of patients with increased thickness of the mucus layer [5]. There is some indirect evidence that two-phase gas–liquid flow occurs commonly in tracheal tubes containing a luminal biofilm [6], but the atomization and trajectory of biofilm particles in patients undergoing mechanical ventilation has not yet received detailed attention. An indwelling tracheal tube may increase substantially the likelihood of propulsion of atomized tracheal tube biofilm into the lungs, by bypassing the inertial impaction filter system of the upper respiratory tract in these patients.

This simulation study suggests that low viscosity biofilm particles small enough to reach far into the lung can be disseminated with a velocity sufficient to

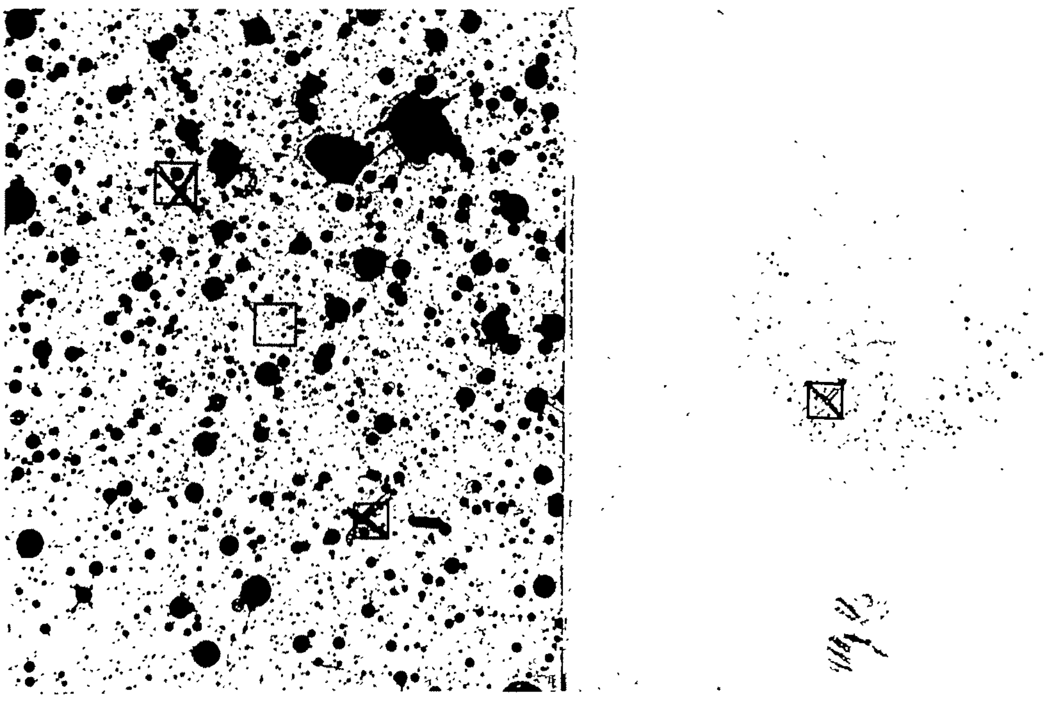


FIG. 3. Ink particle scatter obtained before (left) and after (right) placement of a bifurcating tube between the tracheal tube tip and a sheet of glass.

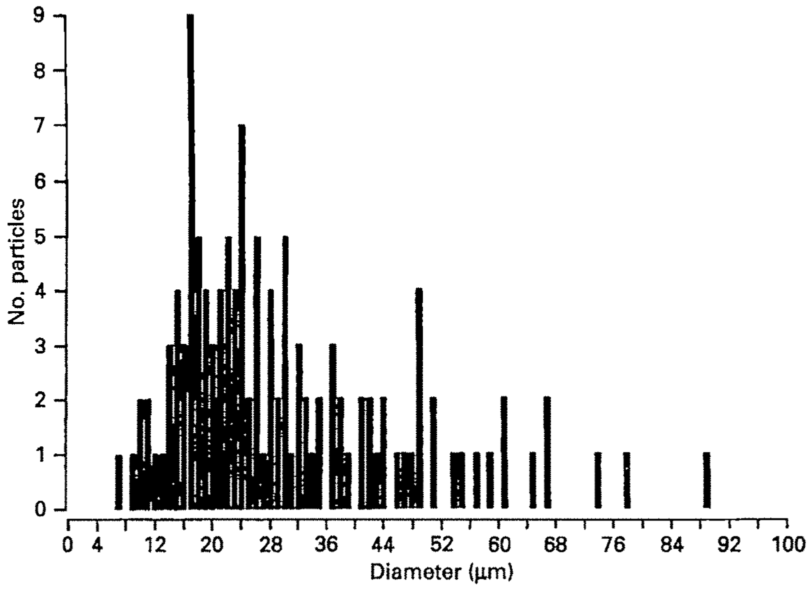


FIG. 4. Size distribution (*D* value) histogram of ink spots obtained in a 2.5 × 2.5-mm area on glass scatter plate after passage through bifurcating tube.

traverse the first order bifurcation in a model of an intubated trachea with symmetrically branched main "bronchi". The size of spots obtained in this series of experiments may overestimate particle size, because there may be some degree of particle spread at the moment of impact. A study of deposition of nebulized aerosols in spontaneously breathing volunteers found that 44% nebulizer contents reached the lungs when the particle size was 10.3 μm mass median diameter [7]. In this study, percentage deposition increased with decreasing aerosol particle size. In another radiolabelled particle deposition study, particles of 0.5–2 μm (approximately the size of single bacterial cells) were found to reach the alveoli without significant loss, whereas particles > 12 μm were not able to penetrate the alveoli [8]. The various equations used to predict particle deposition in the Weibel morphological model of the human lung have been applied to inhalation of particles in the 5-μm range [9], which would be expected to result in maximum deposition at the segmental and subsegmental bronchial level. If these results can be applied to particles entrained from tracheal tube biofilm, the majority would not be expected to penetrate further than this level; however, altered gas flow pathway and pattern expected during mechanical ventilation may alter substantially particle deposition.

The process by which particles are produced in the tube can be described as gas–liquid interaction, in which the degree of interaction is sufficient to cause fracture of a gas–liquid interface (the luminal biofilm surface) with onward propulsion of liquid particles by the gas phase. Physical factors governing gas–liquid interaction in tubes with a liquid lining have been determined previously, and it was shown that the minimum thickness of liquid lining layer required for gas–liquid interaction was 0.5 mm [10]. The critical flow required to generate gas–liquid interaction in an 8.5-mm i.d. tube with a 0.5-mm liquid lining layer is equivalent to a Reynolds number of > 4000. A Reynolds number of 2000, synonymous with turbulent flow, is achieved readily in a tube of this size during mechanical ventilation, and at a flow of 1 litre s^{-1} the Reynolds number is more than 7000. This greater Reynolds number indicates a greater energy loss through gas–liquid interaction, with fluid expulsion from the tracheal tube and the production of mist or particle flow [11].

An important determinant of particle entrainment is the viscosity of the lining liquid. In clinical practice, tracheal tube biofilm is a heterogenous matrix and a wide range of liquid viscosity would be expected in a single biofilm. The biofilm layer adjacent to the luminal surface and therefore most subject to fragmentation is also likely to be the least viscous, because of factors such as condensation of humidifier water and the instillation of saline during tracheal suction procedures. The simulation experiments described in the present study were conducted therefore with a liquid of viscosity similar to that of water. More viscous biofilms are less likely to undergo fragmentation under the same conditions.

Our results provide evidence to suggest that gas–liquid interaction in the tracheal tube provides an effective means of disseminating particles into the ventilated lung. Further work on particle entrainment and scatter from tracheal tube biofilm under different conditions of gas flow is required. The dissemination of bacteria and other components of tracheal tube biofilm as a result of physical processes occurring in the tracheal tube requires consideration as a possible step in the pathogenesis of nosocomial pneumonia.

REFERENCES

1. Sottile FD, Marrie TJ, Prough DS, Hobgood CD, Gowr DJ, Webb LX, Costerton JW, Gristina AG. Nosocomial pulmonary infection: possible etiological significance of bacterial adhesion to endotracheal tubes. *Critical Care Medicine* 1986; 14: 265–270.
2. Inglis TJJ, Millar MR, Jones JG, Robinson DA. Tracheal

tube biofilm as a source of bacterial colonization of the lung. *Journal of Clinical Microbiology* 1989; **27**: 2014–2018.
3. Weibel ER. *Morphometry of the Human Lung*. Berlin: Springer-Verlag, 1963.
4. Swift DL. Generation and respiratory deposition of therapeutic aerosols. *American Review of Respiratory Diseases* 1980; **122**: 71–77.
5. Kim CS, Rodriguez CR, Eldridge MA, Sackner MA. Criteria for mucus transport in the airways by two-phase gas–liquid flow mechanism. *Journal of Applied Physiology* 1986; **60**: 901–907.
6. Inglis TJJ. Evidence for dynamic phenomena in residual tracheal tube biofilm. *British Journal of Anaesthesia* 1993; **70**: 22–24.
7. Clay MM, Clarke SW. Effect of nebulised aerosol size on lung deposition in patients with mild asthma. *Thorax* 1987; **42**: 190–194.
8. Heyder J. Mechanisms of aerosol particle deposition. *Chest* 1981; **80**: S820–823.
9. Agnew JE, Pavia D, Clarke SW. Aerosol particle impaction in the conducting airways. *Physics in Medicine and Biology* 1984; **29**: 767–777.
10. Clarke SW, Jones JG, Oliver DR. Resistance to two-phase gas–liquid flow in airways. *Journal of Applied Physiology* 1970; **29**: 464–471.
11. Selsby D, Jones JG. Some physiological and clinical aspects of chest physiotherapy. *British Journal of Anaesthesia* 1990; **64**: 621–631.

British Journal of Anaesthesia 1993; **70**: 532–535

EFFECT OF HYPEROXIA ON THE BREATHING OF PATIENTS ANAESTHETIZED WITH INFUSIONS OF PROPOFOL

A. C. DOW AND N. W. GOODMAN

SUMMARY

We have assessed the effects on the pattern of breathing of changing the inspired gas from air to oxygen, by analysing the 15 breaths before and 15 breaths after the change, in 10 patients anaesthetized with propofol. Eight of 14 changes decreased tidal volume ($P < 0.01$) by between 16% and 30%. Nine changes increased ventilatory cycle time ($P < 0.01$) by between 8% and 16%. Total ventilation decreased by between 7% and 33%. The peripheral chemoreceptors are active during propofol anaesthesia, and patients should be able to respond to hypoxia. (Br. J. Anaesth. 1993; **70**: 532–535)

KEY WORDS

Anaesthetics, intravenous: propofol. Ventilation: peripheral chemoreflexes, spontaneous ventilation.

Beddoes suggested to Davy that general anaesthesia depressed respiration; he had noted the "purplish colour of blood flowing from the leeches" that had been placed on patients breathing nitrous oxide [1]. In general, volatile and i.v. anaesthetic agents reduce the ventilatory sensitivity to carbon dioxide; this has been tested usually during hyperoxia, when the sensitivity is mainly of the central chemoreceptors. The response of the peripheral chemoreceptors to hypoxia is depressed by halothane anaesthesia [2], and the peripheral hypoxic response may be more sensitive to general anaesthesia than the central response to carbon dioxide. This discharge of the peripheral chemoreceptors in hypoxia is reduced by propofol anaesthesia in animals [3]; the investigators commented that even "an i.v. dose... smaller than the standard induction dose caused a visible depression of activity in normoxia". Earlier, Duffin, Triscott and Whitwam had studied the ventilatory response to two breaths of 100% oxygen in patients anaesthetized with either halothane or thiopentone [4]. This was applying Dejours' idea [5] that the initial response to hyperoxia is mediated entirely by the chemoreceptors, before there is time for any secondary responses. Five of Duffin's seven patients who received thiopentone had a 10% reduction in total ventilation, occurring about six breaths after the two breaths of oxygen. The patients who received halothane had a smaller, non-significant, reduction in total ventilation. Knill, Bright and Manninen studied the effects of thiopentone [6]: the hypoxic response was unaffected, but the response to carbon dioxide reduced. We have investigated the effect of altering the inspired oxygen concentration on the breathing pattern of patients anaesthetized with propofol.

PATIENTS AND METHODS

Twelve patients gave written informed consent to take part in a continuing study of breathing patterns under anaesthesia, which had been approved by the local Research Ethics Committee. All patients were non-obese, ASA I and with airways judged before operation to be easy to manage. Six patients accepted the offer of premedication with a benzodiazepine.

When the patient arrived in the anaesthetic room, an oximeter probe was placed on the finger and an arterial pressure cuff on the arm. The cuff was not used routinely because of the disturbing influence of cuff inflation on the breathing. Belts for respiratory inductance plethysmography were fitted around the ribcage and abdomen, and the signal was calibrated (see below) before induction of anaesthesia. A 20-gauge cannula was inserted into a vein in the non-dominant arm, and was connected to a propofol infusion. An induction dose of 2–3 mg kg^{-1} was given, and supplementary doses of 20–40 mg if necessary to allow insertion of a laryngeal mask airway. The patient breathed air via a Mapleson A system, with a fresh gas flow of at least 10 litre min^{-1}. Anaesthesia was maintained with a reducing infusion of propofol: 13 mg kg^{-1} h^{-1} for 10 min, 11 mg kg^{-1} h^{-1} for 10 min and finally 9 mg kg^{-1} h^{-1}. In some patients it was necessary to maintain the infusion at a given rate for longer than 10 min. Oxygen was added to the fresh gas flow if the saturation was 90% or less.

A sampling tube for capnography was placed in the right-angle connector of the laryngeal mask airway. Outputs from the capnograph and pulse oximeter were recorded onto the two-channel recorder of the capnograph (Gould Godart Mark III). The respiratory inductance plethysmograph (Respitrace model 10.9000) was calibrated before induction of anaesthesia by double least squares linear regression against a pneumotachograph (Fleisch head: Godart pneumotachograph 17212), itself calibrated

---

ALASDAIR C. DOW, M.B., CH.B., M.R.C.P. (U.K.), F.R.C.ANAES.; NEVILLE W. GOODMAN, M.A., D.PHIL., B.M., B.CH., F.R.C.ANAES.; University Department of Anaesthesia, Medical School Unit, Southmead Hospital, Bristol BS10 5NB. Accepted for Publication: December 15, 1992.

against a 1-litre syringe. The calibration and subsequent analysis were by computer program (BBC B+/Macintosh IIsi running BBC Basic), as reported previously [7]. The inductance plethysmograph was not recalibrated after induction of anaesthesia, but patients were not moved after induction and we were interested, not in absolute values of tidal volume, but only in changes occurring when stimuli were applied in periods of otherwise stable breathing. Signals from the Respitrace, and of capnography from the later patients, were recorded by frequency-modulated tape recorder (Racal Thermionic Store 4).

When there was clinically stable anaesthesia, with no change in the infusion rate over the preceding 100 breaths, the fresh gas flow was changed to 100% oxygen. If time allowed, some of the patients were later exposed again to air, and again to oxygen.

At the end of the study, the inductance belts were removed and the patients were taken into the operating theatre for their scheduled surgery.

Analysis

The maximal reduction in total ventilation after two breaths of oxygen in Duffin's study occurred about six breaths after adjustment of the inspired gas [4]. We therefore ignored six breaths, starting with the breath on which the gas flow was adjusted. We analysed two groups of breaths: the 15 breaths before the change to oxygen, to establish a baseline, and the 15 breaths *after the gap* of six breaths.

Data were transferred to a Macintosh IIsi computer (BBC Basic, FileMac: Human Computer Interface Ltd). Programs written in BBC Basic, running on the Macintosh, were used to prepare text (ASCII) files used as input to a statistical package (StatView SE+Graphics: Abacus Concepts) and a spreadsheet (Excel V3.0: Microsoft).

We analysed tidal volume and ventilatory cycle time formally, and present means and 95% confidence limits on those means. Total ventilation was calculated from tidal volume and cycle time; only the means are presented.

TABLE I. *Mean (95% confidence limits) tidal volume (V_T) for 15 breaths before, and 15 breaths after, the change of fresh gas from air to oxygen in patients anaesthetized with an infusion of propofol. The six breaths immediately after the change have been excluded.* *P < *0.05;* **P < *0.01*

Patient No.	V_T (ml) Before oxygen	After oxygen	Change (%)
9	175 (164–186)	150 (139–161)	−16**
10	177 (171–183)	179 (174–184)	1
10	203 (195–211)	206 (200–212)	2
12	207 (198–216)	208 (199–217)	0
13	172 (159–185)	121 (112–130)	−30**
14	246 (224–268)	190 (176–204)	−23**
15	194 (182–206)	156 (145–167)	−20**
16	220 (210–230)	167 (152–182)	−24**
16	241 (231–251)	199 (191–207)	−17**
18	271 (251–291)	227 (208–246)	−16**
18	326 (288–364)	320 (294–346)	−2
19	216 (193–239)	171 (145–197)	−21**
20	93 (88–98)	85 (80–90)	−9*
20	112 (109–115)	104 (101–107)	−7*

TABLE II. *Mean (95% confidence limits) ventilatory cycle time (T_T) for 15 breaths before, and 15 breaths after, the change of fresh gas from air to 100% oxygen in patients anaesthetized with an infusion of propofol. The six breaths immediately after the change have been excluded.* *P < *0.05;* **P < *0.01*

Patient No.	T_T (ms) Before oxygen	After oxygen	Change (%)
9	3387 (3241–3533)	3707 (3517–3897)	9**
10	3305 (3182–3422)	3659 (3543–3775)	11**
10	3465 (3353–3577)	3902 (3749–4055)	13**
12	2920 (2822–3018)	3153 (3023–3283)	8**
13	2277 (2168–2386)	2392 (2260–2524)	5*
14	3448 (3287–3609)	3985 (3752–4218)	16**
15	2818 (2679–2957)	2865 (2755–2975)	2
16	2687 (2551–2825)	2829 (2708–2950)	5*
16	2942 (2759–3125)	2873 (2736–3010)	−2
18	2566 (2453–2679)	2844 (2544–3144)	11**
18	2735 (2602–2868)	2998 (2900–3096)	10**
19	2441 (2345–2537)	2642 (2528–2756)	8**
20	2021 (1971–2071)	2331 (2231–2431)	15**
20	2312 (2239–2385)	2367 (2291–2443)	2

TABLE III. *Mean total ventilation ($\dot{V}_E$) and saturation by pulse oximetry (Sp_{O_2}) for 15 breaths before, and 15 breaths after, the change of fresh gas from air to 100% oxygen in patients anaesthetized with an infusion of propofol. The six breaths immediately after the change have been excluded*

Patient No.	$\dot{V}_E$ (litre min^{-1}) Before oxygen	After oxygen	Change (%)	Sp_{O_2} at change (%)
9	3.10	2.42	−22	91
10	3.21	2.94	−8	92
10	3.52	3.16	−10	93
12	4.25	3.95	−7	94
13	4.53	3.03	−33	93
14	4.28	2.86	−33	93
15	4.13	3.26	−21	88
16	4.91	3.54	−28	94
16	4.92	4.15	−16	96
18	6.36	4.78	−25	86
18	7.15	6.41	−10	91
19	5.31	3.88	−27	94
20	2.76	2.19	−21	90
20	2.91	2.64	−9	93

RESULTS

One patient remained apnoeic for 15 min after induction of anaesthesia, despite an end-tidal carbon dioxide that reached 7.1%; the study was abandoned. Another patient coughed and developed laryngospasm after induction, and required tracheal intubation. A total of 14 changes was obtained from the other 10 patients.

Acute hyperoxia reduced the tidal volume by up to 30% (table I). Ventilatory cycle time increased by up to 16% (table II); this was caused by prolongation of expiratory time (values not given). Effects on tidal volume and cycle time varied between patients, but total ventilation was reduced in all patients, by between 7% and 33% (table III).

The five records with the greatest changes in total ventilation are shown individually in figure 1 and, to show the time course of the response, are summed in figure 2. The change in total ventilation was maximal by the 11th breath (about 30 s) after the change of

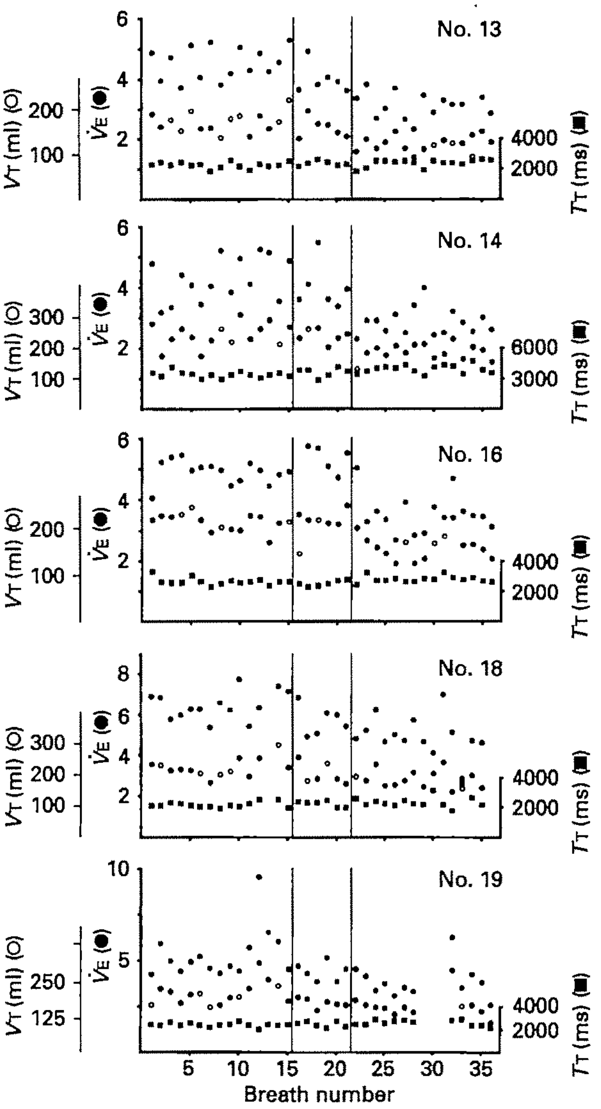


FIG. 1. Tidal volume (V_T: ○), total ventilation ($\dot{V}_E$: ●) (units, omitted for clarity: litre min^{-1}) and ventilatory cycle time (T_T: ■) at the five largest changes in ventilation caused by hyperoxia in patients anaesthetized with an infusion of propofol. The first vertical line indicates when the fresh gas was changed from air to 100% oxygen; the second vertical line marks the start of the 15 breaths used for comparison with the baseline breathing air. Patient number top right. Note that some invalid breaths caused by transient arm movements were deleted: 13 and 36 from patient No. 18; 29–31 from patient No. 19.

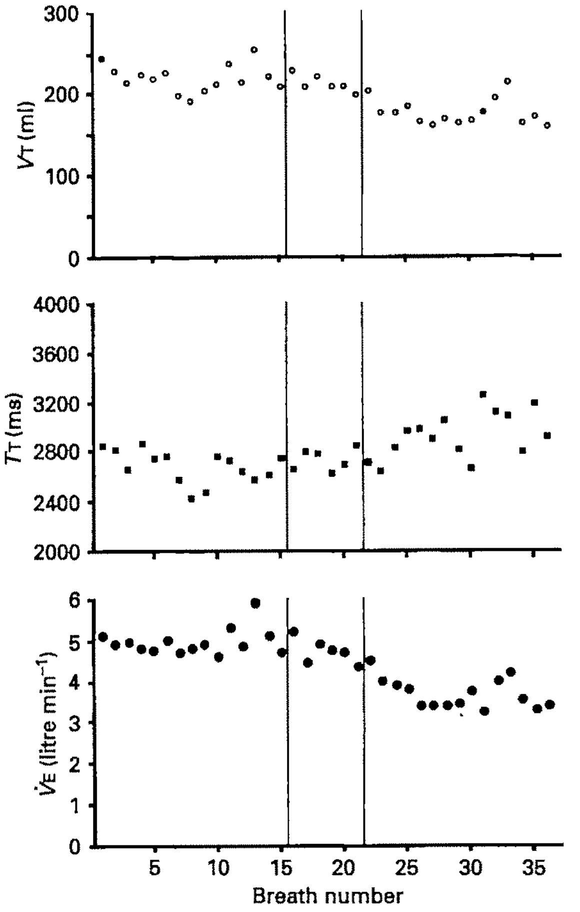


FIG. 2. Mean values for tidal volume (V_T: ○), ventilatory cycle time (T_T: ■) and total ventilation ($\dot{V}_E$: ●) calculated from the five largest changes in ventilation caused by hyperoxia in patients anaesthetized with an infusion of propofol. The first vertical line indicates when the fresh gas was changed from air to 100% oxygen; the second vertical line marks the start of the 15 breaths used for comparison with the baseline breathing air.

gas mixture. The decrease in tidal volume in these summed responses occurred before the increase in cycle time.

DISCUSSION

The ventilatory response to hyperoxia in normal awake humans is complex. The increased arterial partial pressure of oxygen is a mild depressant. At least when applied as a sudden stimulus in awake humans [5], the initial depression of ventilation occurs within a few breaths but, in continuing hyperoxia, the reduced ventilation leads to an increased partial pressure of carbon dioxide, which counters the depression. Hyperoxia and hypercapnia have opposing effects on cerebral vasodilatation [8]. This affects the relation between the arterial carbon dioxide and its partial pressure at the central receptors. It is not just the magnitude of these various effects that is complicated, but the time courses in addition—both of the vascular responses and of the ventilatory ones; the central chemoreceptors, almost entirely responsible for the secondary response to hypercapnia in hyperoxia, react more slowly than the peripheral chemoreceptors [9].

We did not attempt to maintain isocapnia, and a small increase in end-tidal carbon dioxide accompanied many of the changes to breathing oxygen. In some patients, the end-tidal carbon dioxide decreased but became irregular, which was probably an indication that end-tidal gas was not alveolar; there is no reason why arterial carbon dioxide should not have increased with every decrease in ventilation.

Of itself, the change in carbon dioxide should oppose the ventilatory effects of hyperoxia, so does not affect the conclusion that patients anaesthetized with propofol can respond to changes in the partial pressure of oxygen. The response to hyperoxia was rapid: for the five largest responses, the mean tidal volume was already less than any baseline breath by the seventh breath after changing the gas mixture. Increases in cycle time lagged a couple of breaths behind the decreases in tidal volume. The response in resting awake man occurs "after a delay of 10 seconds" [5]. The response in patients anaesthetized with propofol is probably little different, given our unknown delay between changing the gas mixture and the onset of hyperoxia; it take a few seconds for changes of the flowmeter settings to affect the oxygen concentration of the inspired gas.

We did not analyse the ventilation beyond 15 breaths because of the later unpredictable effects. For the same reason, we did not analyse formally the ventilatory effect of switching back from oxygen to air; the partial pressure of oxygen then changes too slowly to have the sudden and unequivocal effect on ventilation of the change from air to oxygen. Fifteen breaths is about 30–50 s at the breathing frequencies of our patients, and secondary effects of hyperoxia would have started in this time. In retrospect, we would have reported much the same findings if we had measured only five breaths after noticing an effect. Part of the problem of analysis was, again, the unknown delay after altering the flowmeters; some patients may have started to respond during the six ignored breaths.

No analysed change of gas mixture was made within 100 breaths (about 4–7 min) of changing the rate of infusion of propofol. We cannot state that anaesthesia was "steady-state", only that the infusion was constant, but depth of anaesthesia should have been stable enough not to confound ventilatory changes measured over 1–2 min around a change of gas mixture. We used only clinical criteria to assess depth of anaesthesia (pattern of ventilation, size of pupils, movement of limbs). The response to hyperoxia may be affected by depth of anaesthesia, but we did not measure plasma concentrations of propofol, so can make no comment. We do not believe that predictions of plasma concentration made from rate of infusion are precise enough in individual patients, and we would not presume that we can correlate our clinical assessments of depth with our patients' responses to hyperoxia.

We conclude from our data and the earlier work of Duffin, Triscott and Whitwam [4] that the early response to hyperoxia was caused by alteration of peripheral chemoreceptor firing. Some reduction in total ventilation occurred at all changes, but the important component of the change was sometimes the decrease in tidal volume and sometimes the increase in cycle time. For only one change (the second change in patient 20) did neither variable alter at the 1% level. Differences in response could have occurred because of differing anaesthetic depth at the changes or differing arterial partial pressures of oxygen in the patients before the hyperoxia [5], but the response to hypoxia varies between individuals. Two of Duffin's seven patients given thiopentone did not respond to hyperoxia [4].

The alterations in both tidal volume (reflecting decreased ventilatory drive) and cycle time (caused by longer expiratory time) are typical of transient chemical stimuli affecting the peripheral chemoreceptors [10]. When the stimulus is mainly of the central chemoreceptors, for instance during hyperoxic rebreathing of carbon dioxide [9], the increase in ventilation is almost entirely because of increased drive [10], certainly in patients anaesthetized with propofol [11].

Ponte and Sadler studied the effect of propofol on the carotid body chemoreceptors of cats and rabbits [3], and observed that an infusion of propofol into the carotid artery abolished chemoreceptor discharge in normoxia and prevented the increase in discharge that occurs in hypoxia. Thiopentone and etomidate did not abolish the response to hypoxia. Their propofol infusion of 1.5–3 mg min^{-1} (90–180 mg h^{-1}) is equivalent to 18–36 mg kg^{-1} h^{-1} (if the animal weight is assumed to be 5 kg), which is a greater rate than that used in the present study. Species differences may also be important.

We suggest that the peripheral chemoreceptors are active during clinical anaesthesia with propofol, and that at least some patients may be able to respond to hypoxia.

REFERENCES

1. Nunn JF. The effect of anaesthesia on respiration. In: Gray TC, Nunn JF, Utting JE, eds. *General Anaesthesia*. London: Butterworths, 1980; 493–509.
2. Knill RL, Gelb AW. Ventilatory responses to hypoxia and hypercapnia during halothane sedation and anesthesia in man. *Anesthesiology* 1978; **49**: 244–251.
3. Ponte J, Sadler CL. Effect of thiopentone, etomidate and propofol on carotid body chemoreceptor activity in the rabbit and the cat. *British Journal of Anaesthesia* 1989; **62**: 41–45.
4. Duffin J, Triscott A, Whitwam JG. The effect of halothane and thiopentone on ventilatory responses mediated by the peripheral chemoreceptors in man. *British Journal of Anaesthesia* 1976; **48**: 975–980.
5. Dejours P. Chemoreflexes in breathing. *Physiological Reviews* 1962; **42**: 335–358.
6. Knill RL, Bright S, Manninen P. Hypoxic ventilatory responses during thiopentone sedation and anaesthesia in man. *Canadian Anaesthetists Society Journal* 1978; **25**: 366–372.
7. Goodman NW, Vanner RG, Wade JA. Effects of incremental doses of alfentanil and propofol on the breathing of anaesthetized patients. *British Journal of Anaesthesia* 1989; **63**: 548–553.
8. Santiago TV, Edelman NH. Brain blood flow and control of breathing. In: Cherniack NS, Widdicombe JG, eds. *Control of Breathing*. Volume II of Fishman AP, ed. *The Respiratory System*. Section 3 of *Handbook of Physiology*. Bethesda: American Physiological Society, 1986; 163–179.
9. Duffin J. The chemoreflex control of breathing and its measurement. *Canadian Journal of Anaesthesia* 1990; **37**: 933–942.
10. Cunningham DJC, Robbins PA, Wolff CB. Integration of respiratory responses to changes in alveolar partial pressures of CO_2 and O_2 and in arterial pH. In: Cherniack NS, Widdicombe JG, eds. *Control of Breathing*. Volume II of Fishman AP, ed. *The Respiratory System*. Section 3 of *Handbook of Physiology*. Bethesda: American Physiological Society, 1986; 475–528.
11. Goodman NW, Black AMS, Carter JA. Some ventilatory effects of propofol as a sole anaesthetic agent. *British Journal of Anaesthesia* 1987; **59**: 1497–1503.

British Journal of Anaesthesia 1993; 70: 536–541

EFFECTS OF ACTIVE AND PASSIVE SIGHS IN NORMOXIA AND HYPEROXIA ON THE BREATHING OF PATIENTS ANAESTHETIZED WITH INFUSIONS OF PROPOFOL

N. W. GOODMAN AND A. C. DOW

SUMMARY

Spontaneous augmented breaths (active sighs) reduced the tidal volume and inspiratory time of succeeding breaths; manual lung inflations (passive sighs) reduced the tidal volume but had little effect on inspiratory time. Sighs in air, whether active or passive, reduced tidal volume more than sighs in hyperoxia (100% oxygen or 33% oxygen in nitrous oxide) after both active and passive sighs (overall difference about 10%); the reduction in inspiratory time after a sigh was less affected by gas mixture. Calculated mean inspiratory flow was reduced after passive sighs, but active sighs were more likely to cause arousal, which complicated the analysis. Tidal volume was reduced after a sigh partly because of reduced peripheral chemoreceptor input, the main effect of which was to reduce inspiratory flow, and partly because inspiratory time was shorter. Although the chemoreceptors may affect inspiratory time after a sigh, the greater effect of active sighs compared with passive sighs makes it likely that the shortening was either part of the neural output that causes spontaneous sighs, or was caused by mechanoreceptor input not mimicked by manual lung inflation. (Br. J. Anaesth. 1993; **70**: 536–541)

KEY WORDS

Anaesthetics, intravenous: propofol. Ventilation: spontaneous sighing, manual lung inflation, peripheral chemoreflexes.

Spontaneous sighs, or augmented breaths [1], transiently change the pattern of breathing. In patients anaesthetized with propofol, the succeeding breaths have shorter inspiratory times and reduced mean inspiratory flows [2], so their tidal volumes are smaller. These changes last about 10 to 20 breaths after the sigh. A sigh causes a transient alteration in the arterial partial pressures of carbon dioxide and oxygen, and these alterations are at least partly the cause of the altered breathing pattern. Khoo and Marmarelis [3] suggested using the response to a sigh to measure the gain of the peripheral chemoreflex. We have investigated the causes of the altered pattern by comparing the effects of spontaneous sighs, which we refer to as "active sighs", with the effects of manual inflations of the lungs, "passive sighs", in patients anaesthetized with propofol and breathing air or hyperoxic mixtures. Our hypothesis was that a sigh in hyperoxia would cause less disturbance than a sigh in air because of reduced peripheral chemoreceptor input; and that from the comparison between active and passive sighs we could show how much of the disturbance was caused by the change in chemical stimulus and how much by other factors.

A preliminary report has been made of this work [4]. Analysis of the effects of hyperoxia on the undisturbed pattern of breathing will be presented separately.

PATIENTS AND METHODS

Patients of slim build and with what we considered easily manageable airways were asked for their consent. We studied 19 patients (16 women), all ASA I, aged 23–52 yr and weighing 49–83 kg. Patients were prescribed a benzodiazepine for premedication if they wished ($n = 9$).

A venous cannula was placed in the non-dominant arm. A probe for pulse oximetry and a cuff for a non-invasive monitor of arterial pressure were attached. We did not intend to measure arterial pressure unless we were unhappy with the clinical condition of the patient, because of the inevitable disturbance to the breathing caused by arousal when the cuff inflates. Anaesthesia was induced with propofol and a laryngeal mask airway was inserted. Anaesthesia was maintained by a three-step reducing infusion starting at 13 mg kg^{-1} h^{-1}, stepping after 10-min intervals to 11 mg kg^{-1} h^{-1}, and then to 9 mg kg^{-1} h^{-1}. The interval was prolonged if patients were lightly anaesthetized clinically. Patients started by breathing air and were later changed to breathing oxygen, or started by breathing oxygen and later breathed 33% oxygen in nitrous oxide. We used a Mapleson A system with flows of at least 10 litre min^{-1}. We did not change gas mixture or infusion rate within at least 100 breaths (about 5 min) of the other's being changed, except to add oxygen 1–2 litre min^{-1} if the saturation was less than 90%. This was necessary for a short time after induction when patients were breathing air, but for only two of these patients later during any study. On more than one occasion, changing from a finger to an ear probe improved the apparent saturation.

NEVILLE W. GOODMAN, M.A., D.PHIL., B.M., B.CH., F.R.C.ANAES.; ALASDAIR C. DOW, M.B., CH.B., M.R.C.P.(U.K.), F.R.C.ANAES.; University Department of Anaesthesia, Medical School Unit, Southmead Hospital, Bristol BS10 5NB. Accepted for Publication: December 15, 1992.

TABLE I. *Spontaneous augmented breaths (active sighs) in patients anaesthetized with propofol and breathing different gas mixtures (mean* (SD) *[range] or mean (95% CL)). Values are normalized to the mean of the five breaths preceding the sigh.* V_T = *Tidal volume;* T_I = *inspiratory time;* T_E = *expiratory time; IF = inspiratory flow*

	V_T of sigh	T_I of sigh	T_E of sigh	V_T of next 5 breaths	T_I of next 5 breaths	T_E of next 5 breaths	Mean IF (V_T/T_I) of next 5 breaths
All	2.70 (0.95)	1.39 (0.24)	1.45 (0.35)	0.92	0.92	1.00	1.00
($n = 33$)	[1.67–5.16]	[0.91–2.26]	[0.90–2.49]	(0.88–0.97)	(0.90–0.94)	(0.97–1.04)	
Air	3.44 (0.95)	—	—	0.81	0.91	1.12	0.88
($n = 9$)	[3.31–5.16]			(0.69–0.93)	(0.86–0.97)	(1.02–1.21)	
N_2O/O_2	2.01 (0.41)	—	—	0.98	0.94	0.96	1.05
($n = 12$)	[1.67–3.04]			(0.94–1.02)	(0.92–0.96)	(0.92–1.00)	
O_2	2.84 (0.88)	—	—	0.95	0.92	0.96	1.04
($n = 12$)	[1.69–4.65]			(0.90–1.00)	(0.89–0.95)	(0.92–0.99)	

If a patient sighed, we waited 30 breaths and then gave a matching passive sigh by squeezing the reservoir bag, while the patient was breathing in, to augment that breath to about the same tidal volume as the active sigh; otherwise we aimed for a passive sigh about 2.5 times the average tidal volume. In each patient, we aimed for one pair of sighs (one active and one passive) on the first gas mixture, and one pair on the other. If there was time, we changed gas mixtures again.

Breathing was recorded by respiratory inductance plethysmography (Respitrace model 10.9000), calibrated before induction of anaesthesia by double least squares linear regression against a pneumotachograph (Fleisch head: Godart pneumotachograph 17212), itself calibrated against a 1-litre syringe. The calibration and subsequent analysis were by computer program (BBC B+/Macintosh IIsi running BBC Basic), as reported previously [5]. The inductance plethysmograph was not recalibrated after induction of anaesthesia, but patients were not moved after induction and all comparisons of ventilatory variables were made within patient, or were normalized to a baseline before comparisons were made between patients.

Output from the Respitrace was recorded on magnetic tape (Racal Thermionic Store 4). A continuous capnogram was recorded (Gould Godart Mark III) on paper and on a channel of the tape recorder. Initially, saturation was recorded by hand with other experimental observations; for later patients the signal was recorded onto the second channel of the capnograph pen recorder.

Analysis

The change in tidal volume after a sigh is to about 70% of its preceding mean; the SD of tidal volume is about 10% of mean in the anaesthetized patient, but this variability is approximately doubled after a sigh [2]. From these figures, we estimated that we would need about 60 sighs if we were expecting to distinguish the halving of the effect of a sigh. Inevitably this was arbitrary, as we did not known what to expect, but we decided to wait until we had this number of analysable sighs before any analysis. The first 15 patients yielded 58 sighs, from which the form of the results could be seen. We studied another four patients before deciding to complete the analysis.

For each sigh, we looked at the tidal volume, inspiratory time and expiratory time of the 10 preceding breaths, the sighs and the 20 succeeding breaths. For the active sighs, we also looked at abdominal contribution. We normalized each sigh to the mean of each variable for the five breaths preceding each sigh. The normalized breaths from all analysed sighs were pooled to give normalized means and 95% confidence limits (*t* distribution) on those means. For any given pooled breath, therefore, a mean was significantly different ($P < 0.05$) from baseline if its 95% confidence limits did not include unity. Results are given as fractional values—that is, if a variable is given as 0.72, it is 72% of baseline.

Instead of multiple testing breath-by-breath, we used a summary measure of the effect of each sigh by taking a further mean value of the first group of five (normalized) succeeding breaths. Comparisons on pooled data were made by estimating confidence intervals on differences; comparisons on paired data (active sigh on air with passive sigh on air, or active sigh on air with active sigh on oxygen, from the same patient) were by Wilcoxon matched pairs signed rank test.

Correlation of size of sigh with response to the sigh was checked by a scatter plot and tested formally by Spearman Rank correlation.

StatView (SE+Graphics: Abacus Concepts) was used for standard statistical calculations, and Excel (V3.0: Microsoft) for array calculations, on a Macintosh IIsi computer.

RESULTS

We recorded 46 active sighs and 44 passive sighs. Thirty-three active sighs and 37 passive sighs were analysable. Because we did not manage strict matched pairs (see Patients and Methods) of analysable sighs in all patients, our main analysis was of unpaired comparisons. Figures 2–4 are the pooled observations breath-by-breath; tables I and II are the summary observations, giving details of the sighs and of the group of five succeeding breaths.

Comparison between active and passive sighs

Overall, active and passive sighs were of similar tidal volumes, but the tidal volumes of the active sighs were largest with patients breathing air and smallest with patients breathing nitrous oxide in

TABLE II. *Manual lung inflations (passive sighs) in patients anaesthetized with propofol and breathing different gas mixtures (mean (SD) [range] or mean (95% CL)). Values are normalized to the mean of the five breaths preceding the sigh.* VT = *tidal volume;* TI = *inspiratory time;* TE = *expiratory time; IF = inspiratory flow*

	*V*T of sigh	*T*I of sigh	*T*E of sigh	*V*T of next 5 breaths	*T*I of next 5 breaths	*T*E of next 5 breaths	Mean IF (*V*T/*T*I) of next 5 breaths
All	2.42 (0.38)	1.11 (0.23)	1.18 (0.18)	0.92	0.98	1.03	0.95
($n = 37$)	[2.03–3.60]	[0.67–1.76]	[0.85–1.79]	(0.89–0.95)	(0.96–0.99)	(1.00–1.06)	
Air	2.51 (0.49)	—	—	0.84	0.96	1.06	0.88
($n = 10$)	[2.04–3.36]			(0.76–0.93)	(0.93–0.98)	(1.01–1.11)	
N_2O/O_2	2.62 (0.29)	—	—	0.96	1.00	1.03	0.95
($n = 11$)	[2.04–3.00]			(0.92–0.99)	(0.98–1.03)	(0.96–1.09)	
O_2	2.70 (0.43)	—	—	0.95	0.97	1.01	0.98
($n = 16$)	[2.03–3.60]			(0.91–0.98)	(0.94–1.00)	(0.96–1.05)	

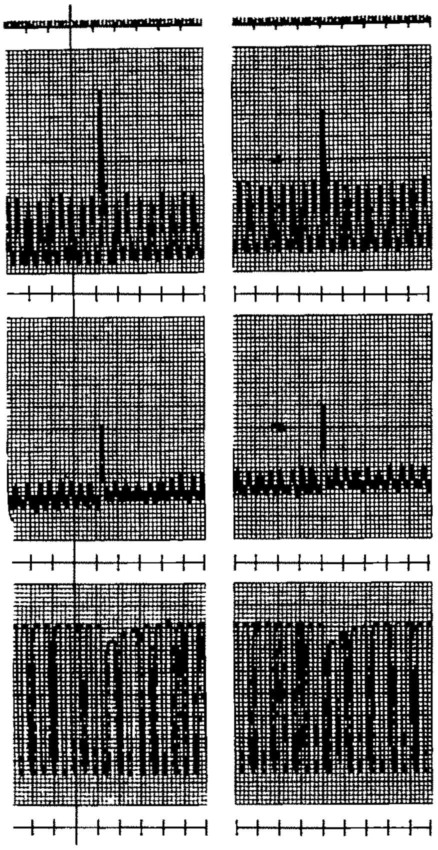


FIG. 1. A spontaneous augmented breath (active sigh), and a manual inflation (passive sigh) in a patient anaesthetized with propofol and breathing air. Top trace: time (seconds). Middle two: rib cage and abdominal output (uncalibrated, with inspiration upwards) from respiratory inductance plethysmography. Lower: capnogram (minimum is zero %, 1 large square = 1%). Thirty breaths (about 1.5 min) separated the sighs. The active sigh was 2.95 × baseline; the mean of the five succeeding tidal volumes 0.84. The passive sigh was 2.67 × baseline; the mean of the five succeeding tidal volumes 0.87.

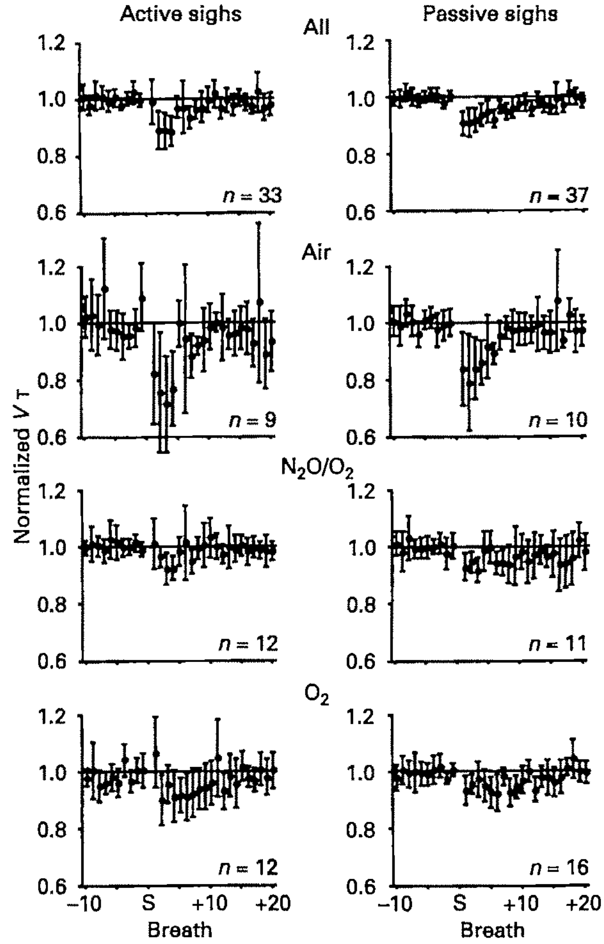


FIG. 2. Effect on tidal volume of active and passive sighs under propofol anaesthesia when breathing air and in hyperoxia. Breaths have each been normalized to the mean tidal volume of the preceding five breaths. Each point and error bar are the means and 95% confidence limits on those means calculated from the summed normalized breaths. The actual sighs are omitted.

oxygen (table I). The tidal volumes of the passive sighs were not different between gas mixtures (table II). We have given only the overall figures for inspiratory and expiratory times of the sighs; both were prolonged more by active than by passive sighs (tables I, II).

Within the limits of measurement, active and passive sighs of similar tidal volume caused similar changes in end-tidal partial pressure of carbon dioxide (fig. 1). The tidal volume of active sighs correlated with the mean tidal volume of the next five breaths (Spearman's $\rho = -0.46$; $P < 0.01$); there was no corresponding correlation for passive sighs (Spearman's $\rho = -0.08$; $P = 0.6$).

The abdominal contribution to the active sighs was 63–127% of baseline, with a mean of 94% (95% CL = 89–99%).

Tidal volume was reduced by about the same amount after active or passive sighs (fig. 2), but inspiratory time was reduced more after an active

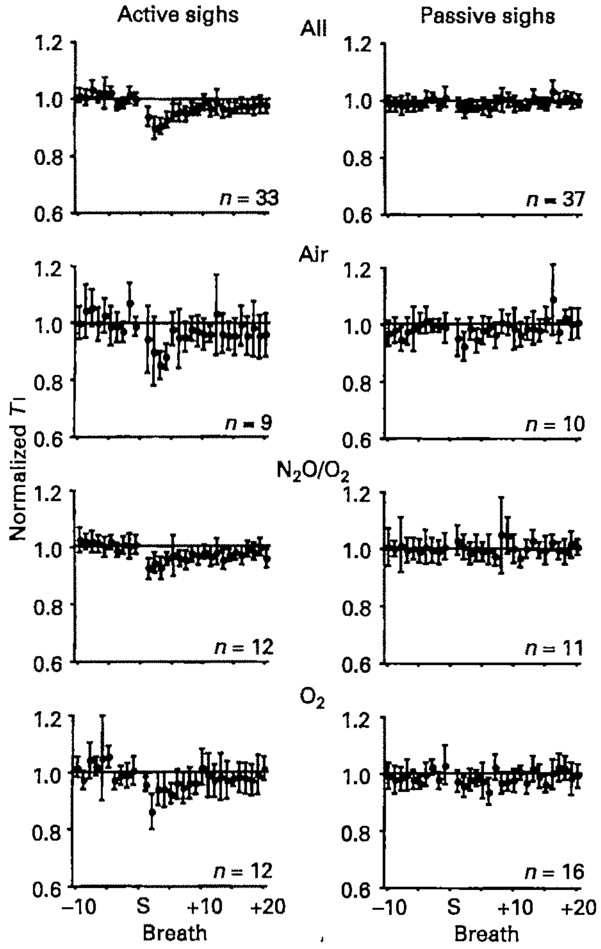


FIG. 3. Effect on inspiratory time of active and passive sighs under propofol anaesthesia when breathing air and in hyperoxia. Breaths have each been normalized to the mean inspiratory time for the preceding five breaths. Each point and error bar are the means and 95 % confidence limits on those means calculated from the summed normalized breaths. The actual sighs are omitted.

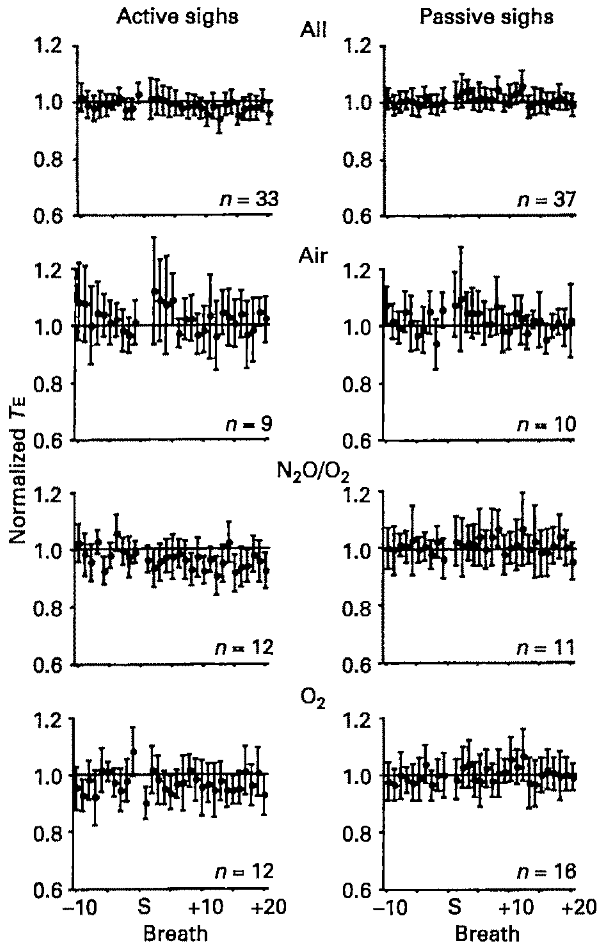


FIG. 4. Effect on expiratory time of active and passive sighs under propofol anaesthesia when breathing air and in hyperoxia. Breaths have each been normalized to the mean expiratory time for the preceding five breaths. Each point and error bar are the means and 95 % confidence limits on those means calculated from the summed normalized breaths. The actual sighs are omitted.

than a passive sigh (fig. 3). Expiratory time is more variable and effects were not so easy to distinguish (fig. 4).

Comparisons between gas mixtures

Sighs, whether active or passive, had more effect on tidal volume when patients were breathing air than when they were breathing 67 % nitrous oxide in oxygen (fig. 2). For active sighs, the difference was 0.17 (95 % CL 0.07–0.27; $P < 0.001$); for passive sighs, the difference was 0.11 (95 % CL 0.03–0.19; $P < 0.01$). There was a similar difference between sighs breathing air and breathing 100 % oxygen. For active sighs, the difference was 0.14 (95 % CL 0.03–0.25; $P < 0.01$); for passive sighs, the difference was 0.10 (95 % CL 0.03–0.17; $P < 0.01$). Sighs with all three gas mixtures affected inspiratory time more if the sigh was active (fig. 3). Only sighs with air prolonged expiratory time, with the same proviso as above concerning variability (fig. 4).

TABLE III. *Paired comparisons of spontaneous augmented breaths (active sighs: AS) and manual lung inflations (passive sighs: PS) in patients anaesthetized with propofol and breathing air or a hyperoxic mixture (ox). Values are normalized to the mean of the five breaths preceding the sigh. The number of comparisons is shown (n), and for each paired comparison: the means, the difference between the means, and the probability by Wilcoxon matched pairs signed rank test.* V_T = *tidal volume;* T_I = *inspiratory time;* T_E = *expiratory time*

$n = 7$	AS:air	PS:air	Diff.	*P*	$n = 17$	AS:ox.	PS:ox.	Diff.	*P*
V_T	0.84	0.86	−0.02	0.53	V_T	0.96	0.95	0.01	0.86
T_I	0.92	0.97	−0.05	0.13	T_I	0.93	0.99	−0.06	0.01
T_E	1.09	1.04	0.05	0.27	T_E	0.95	1.01	−0.06	0.01
$n = 5$	AS:air	AS:ox.	Diff.	*P*	$n = 6$	PS:air	PS:ox.	Diff.	*P*
V_T	0.84	0.96	−0.12	0.23	V_T	0.86	0.95	−0.09	0.04
T_I	0.92	0.94	−0.02	1.00	T_I	0.96	0.98	−0.02	0.07
T_E	1.10	0.95	0.15	0.14	T_E	1.03	1.01	0.02	0.25

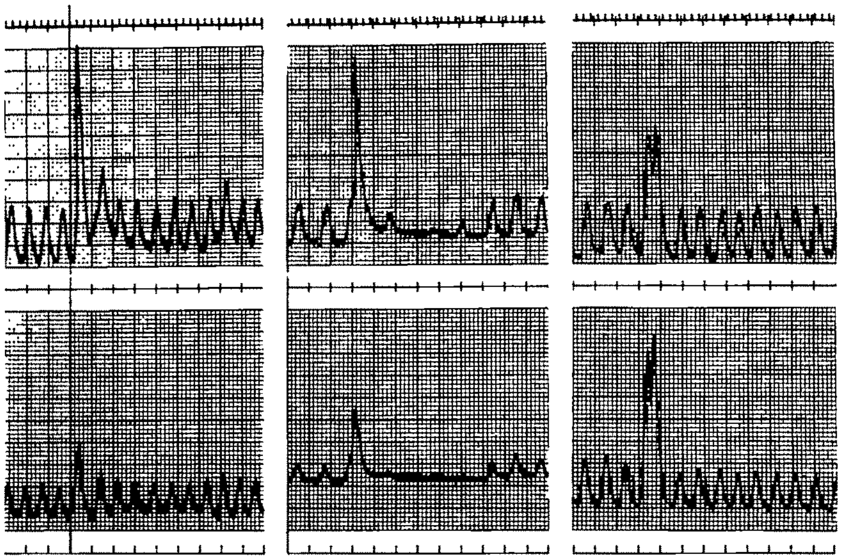


FIG. 5. Three sighs not included in the analysis; patients anaesthetized with propofol and breathing air. Top traces: time (s); middle and lower traces: rib cage and abdominal output (uncalibrated, with inspiration upwards) from respiratory inductance plethysmography. Left: a manual inflation (passive sigh) has caused arousal; the succeeding breath has an increased tidal volume. Middle: A spontaneous augmented breath (active sigh) has caused a short period of virtual apnoea. Right: A passive sigh has triggered an active sigh.

Mean inspiratory flow (calculated as mean tidal volume divided by mean inspiratory time) was reduced after sighs with air but was *greater* for the five succeeding breaths of an active sigh with a hyperoxic mixture.

Paired comparisons

We were able to compare four groups of paired sighs: active sighs on air and passive sighs on air ($n = 7$, from five patients); active sighs with hyperoxic mixtures and passive sighs with hyperoxic mixtures ($n = 17$, from 13 patients); active sighs with air and active sighs with hyperoxic mixtures ($n = 5$, from four patients); and passive sighs with air and passive sighs with hyperoxic mixtures ($n = 6$, from five patients) (table III). Although small numbers make comparisons imprecise, the trend of the paired comparisons for tidal volume and inspiratory time supports the pooled data, in that tidal volume was affected by gas mixture more than by type of sigh and inspiratory time was affected more by type of sigh than by gas mixture. The change in expiratory time was inconsistent: active sighs with air prolonged expiratory time more than passive sighs with air, and active sighs with oxygen *decreased* expiratory time.

Sighs not included for analysis

Twenty sighs were not analysed (13 of them active sighs). Eight were part of—or triggered—an obvious arousal reaction (fig. 5, left), in which there was limb movement or transient tachycardia. Two sighs caused a short apnoea (fig. 5, middle). One passive sigh triggered an active sigh (fig. 5, right), and was excluded. Two active sighs occurred too soon after a change of gas mixture. Two could not be analysed because of sudden shifts in the Respitrace signal shortly after the sighs. The other five excluded sighs occurred when breathing was unstable or irregular, and the sigh was imposed on a pattern of changing tidal volume.

DISCUSSION

The alteration in breathing pattern caused by sighs was, in general, much as described previously [2]. The similarity of reduction in tidal volume after active and passive sighs, and the way this reduction was less in hyperoxia, supports the hypothesis that the reduction is mediated by the chemoreceptors.

As in the previous study [2], most (16 of 19) of our patients were women. We did not record stage of menstrual cycle, or if they were receiving oral contraceptives, so can make no comment on whether differences between patients were influenced in any way by progestagens.

Active sighs shortened inspiratory time more than passive sighs did, and gas mixture had less effect on inspiratory time than on tidal volume. We cannot say that the change in chemoreceptor input had no effect on inspiratory time (there may be some difference between the effect of passive sighs in air and in hyperoxia), but we suggest that much of the effect on inspiratory time is either an in-built response of the respiratory centre when the sigh is generated, or caused by a mechanoreceptor afferent response not mimicked by a passive sigh.

We could not distinguish an effect of nitrous oxide on the pattern after the sigh. Active sighs with nitrous oxide had smaller tidal volumes than sighs with either air or oxygen. We cannot say if this was because of the nitrous oxide. Overall, hyperoxic active sighs had smaller tidal volumes than active sighs with air, which could have affected the tidal volume response to the sigh. As tidal volume was also affected more after a passive sigh with air, when the tidal volumes of the actual sighs were not affected by gas mixture, we believe that hyperoxia does modify the tidal volume response.

What is clear from this study, and which we did not notice during the previous work, is that a sigh can cause, or is part of, arousal. One difference from the previous study [2] was the use of the laryngeal mask airway. Afferents from the larynx form part of many reflexes in the control of breathing. It is unlikely that the laryngeal mask alters the general pattern of the response to sighs—our observations of the effect of active sighs was much the same in this study as in the previous one—but perhaps a sigh is more likely to cause arousal if there is a laryngeal mask in place. Arousal, easy to identify when accompanied by an increase in heart rate occurring with the sigh and continuing for a few beats, complicates analysis of the effects of sighs. The chemical change reduces the tidal volume, but arousal increases it, and there is no easy way of distinguishing between these opposing effects. If there was obvious arousal, we did not include that sigh in the analysis. Arousal was more common with active sighs than with passive sighs. When the arousal had subsided, breaths then followed the usual post-sigh pattern, but the smallest tidal volume after a sigh was the third or fourth breath or later. We suggest that the increase in mean inspiratory flow after hyperoxic *active* sighs was caused by this arousal, and that the decrease in flow after hyperoxic *passive* sighs is a truer reflection of the effect of the change in chemical stimulus: less than occurs with air. In work on cats [6], the rate of increase in phrenic activity after spontaneous and provoked sighs was usually greater and the inspiratory time shorter after the sigh; this study did not include the effect of simple passive inflations.

There was correlation between the tidal volume of active sighs, but not of passive sighs, with the subsequent effect on tidal volume, which we suggest is because of the wider range of tidal volumes of active sighs. There are many sources of variability between tidal volume of sigh and effect: the calibration of inductance plethysmography varies with tidal volume; the end-tidal measurement of carbon dioxide is not the arterial partial pressure; and chemoreceptor reflex sensitivity varies between individuals.

As previously [2], the effect of sighs on expiratory time was unclear, partly because of its greater variability. The only unreported observation on expiratory time in anaesthetized patients about which we are certain is that the expiratory time *of* a passive sigh—of the breath on which it is imposed—is usually prolonged: the next breath is delayed. Bowes, Andrey and Kozar [7] reported in dogs that this prolongation did not occur if the carotid bodies were denervated. We saw no differences in the expiratory times of passive sighs between gas mixtures.

That a sigh can cause arousal, which then affects the ventilatory drive of a breath or two after the sigh, is another reason why the suggestion of Khoo and Marmarelis [3], of using the effect of a sigh to estimate the gain of the peripheral chemoreflex, might not be easy to apply to anaesthetized man.

REFERENCES

1. Glogowska M, Richardson PS, Widdicombe JG, Winning AJ. The role of the vagus nerves, peripheral chemoreceptors and other afferent pathways in the genesis of augmented breaths in cats and rabbits. *Respiration Physiology* 1972; **16**: 179–196.
2. Goodman NW, Kestin IG. Sighs and their effect on the breathing of patients anaesthetized with infusions of propofol. *British Journal of Anaesthesia* 1992; **68**: 48–53.
3. Khoo MCK, Marmarelis VZ. Estimates of peripheral chemoreflex gain from spontaneous sigh responses. *Annals of Biomedical Engineering* 1989; **17**: 557–570.
4. Dow AC, Goodman NW. A comparison of spontaneous sighs and manual inflations breathing air and hyperoxic mixtures. *British Journal of Anaesthesia* 1993; **70**: 474P.
5. Goodman NW, Vanner RG, Wade JA. Effects of incremental doses of alfentanil and propofol on the breathing of anaesthetized patients. *British Journal of Anaesthesia* 1989; **63**: 548–553.
6. Cherniack NS, von Euler C, Glogowska M, Homma I. Characteristics and rate of occurrence of spontaneous and provoked augmented breaths. *Acta Physiologica Scandinavica* 1981; **111**: 349–360.
7. Bowes G, Andrey SM, Kozar LF. Carotid chemoreceptor regulation of expiratory duration. *Journal of Applied Physiology: Respiration, Environmental and Exercise Physiology* 1983; **54**: 1195–1201.

British Journal of Anaesthesia 1993; **70**: 542–545

I.V. ANAESTHESIA WITH PROPOFOL USING A TARGET-CONTROLLED INFUSION SYSTEM: COMPARISON WITH INHALATION ANAESTHESIA FOR GENERAL SURGICAL PROCEDURES IN CHILDREN

E. DOYLE, W. McFADZEAN AND N. S. MORTON

SUMMARY

We studied 40 children undergoing general surgical procedures. They were allocated randomly to receive induction of anaesthesia with propofol 3–5 mg kg^{-1} followed by maintenance with halothane and an appropriate regional block, or induction and maintenance of anaesthesia with a computerized, target-controlled infusion of propofol with a regional block. All patients breathed a mixture of 67% nitrous oxide in oxygen via a laryngeal mask airway. Both techniques provided adequate anaesthesia and operating conditions. There were no significant differences between the groups in heart rate, mean arterial pressure and end-expired carbon dioxide concentration during anaesthesia. There was no significant difference in the recovery times of the two groups. (Br. J. Anaesth. 1993; **70**: 542–545)

KEY WORDS

Anaesthesia: paediatric. Anaesthetic techniques: intravenous infusion. Anaesthetics, intravenous: propofol.

Propofol is associated with prompt, rapid recovery from anaesthesia when used as an induction agent in adults [1]. Compared with induction of anaesthesia with thiopentone, propofol produces earlier return of clinical indices of recovery, protective reflexes and psychomotor function [2, 3], but these differences are not observed if anaesthesia is maintained for more than 30 min using halothane [4].

In paediatric practice, it has been shown that children undergoing day-case surgical procedures under general anaesthesia with isoflurane, with or without regional block, recover more quickly if their anaesthesia is induced with propofol than with thiopentone [5, 6]. Other paediatric studies have compared propofol for both induction and maintenance of anaesthesia with thiopentone induction and maintenance with a volatile agent [7, 8]. These studies in dental and E.N.T. surgery found that propofol compared well with inhalation maintenance and produced significantly quicker recovery from anaesthesia. In a day-case study [8] there was a shorter time to discharge in the propofol group.

A standard technique for many brief general surgical procedures in children is to combine a general anaesthetic with an appropriate regional block to provide perioperative analgesia. This study was designed to compare a technique of induction and maintenance of anaesthesia using a propofol infusion combined with regional block, and a technique of induction with propofol followed by maintenance using halothane combined with a regional block.

PATIENTS AND METHODS

The study was approved by the local Ethics Committee and informed written parental consent was obtained. We studied 40 children of ASA grades I and II undergoing general surgical procedures expected to last less than 1 h. Exclusion criteria included age less than 1 yr, weight less than 10 kg, allergy to eggs and a surgical procedure for which an appropriate regional block could not be performed.

TABLE I. *Patient data and details of operations in groups H (halothane maintenance) and P (propofol maintenance) (number or mean (range))*

	Group H	Group P
Sex (M/F)	19/1	17/3
Age (months)	67.6 (16–154)	66.0 (13–141)
Weight (kg)	20.7 (12.5–32.0)	20.3 (10.2–40.3)
Duration of anaesth. (min)	30.6 (9–52)	33.3 (11–60)
Time end of agent to end surgery (min)	6.2 (2–10)	5.3 (3–8)
Operation		
Orchidopexy	7	7
Circumcision	6	3
Hernia repair	4	6
Otoplasty	1	2
Body surface	2	2
Regional block		
Caudal	13	6
Ilioinguinal	3	9
Penile	1	1
Infiltration	3	4

EDWARD DOYLE, F.R.C.ANAES.; WILLIAM MCFADZEAN*, F.F.A.R.C.S.I.; NEIL S. MORTON, F.R.C.ANAES.; Department of Anaesthesia, Royal Hospital for Sick Children, Yorkhill, Glasgow G3 8SJ. Accepted for Publication: November 25, 1992.

*Present address: Military Hospital, Aldershot, Hants GU11 2AN.

Correspondence to E.D.

Premedication comprised EMLA cream (lignocaine 25 mg g^{-1} and prilocaine 25 mg g^{-1}) applied to the backs of both hands at least 1 h before induction. In the anaesthetic room, pre-induction measurements of heart rate, arterial pressure and arterial oxygen saturation were obtained using a Dinamap non-invasive arterial pressure monitor with an appropriate size of cuff and a Nellcor pulse oximeter. A suitable vein was cannulated with a 22- or 24-gauge cannula.

Patients were allocated randomly (by computer-generated list) to two groups of 20 patients each. Group H (halothane maintenance) received an induction dose of propofol 3–5 mg kg^{-1} (with lignocaine 0.2 mg kg^{-1}) followed by maintenance of anaesthesia with 67 % nitrous oxide and 0.5–2.0 % halothane in oxygen as necessary to maintain an adequate depth of anaesthesia. In group P (propofol maintenance), anaesthesia was induced and maintained with an infusion of propofol delivered by an Ohmeda 9000 infusion pump driven by a Psion II computer containing a program designed to achieve and maintain preselected blood concentrations of propofol [9, 10]. The initial blood targets chosen were in the range 8–14 μg ml^{-1} and these were reduced subsequently to maintain an adequate depth of anaesthesia. These patients breathed a mixture of 67 % nitrous oxide in oxygen. Episodes of apnoea, cough, hiccup and involuntary movements which occurred during induction were noted.

In all patients, a laryngeal mask airway of appropriate size was used to maintain the airway during anaesthesia. An appropriate regional block was performed after induction of anaesthesia and before the start of surgery.

In both groups, measurements of heart rate, arterial pressure and arterial oxygen saturation were taken at 1, 2, 3, 4, 5, 10 and 15 min after induction and at further 5-min intervals until the end of surgery. End-expired carbon dioxide concentration was measured using a Datex Capnomac Ultima when the patient had been moved into theatre and was recorded at 5-min intervals until the end of surgery. Anaesthetic agents were discontinued at the start of skin closure. At the end of surgery, patients were transferred to the recovery area breathing 100 % oxygen via the laryngeal mask airway, which was removed after return of the gag reflex. The time of spontaneous eye opening was noted in the recovery area.

Before the patient was discharged to the surgical ward, the level of comfort and analgesia were assessed clinically.

Data were analysed statistically using Student's *t* test for normally distributed data and the Wilcoxon two-sample rank sum distribution for non-parametric data.

RESULTS

The two groups were similar in age, weight and operative details (table I). The mean dose of propofol required to induce anaesthesia in group H was 3.9 mg kg^{-1} (range 3.0–5.1 mg kg^{-1}). In group P the mean induction bolus of propofol was 3.9 mg kg^{-1} (range 2.8–5.1 mg kg^{-1}) and infusion rates of propofol for maintenance of anaesthesia ranged from 18.3 mg kg^{-1} h^{-1} to 36.2 mg kg^{-1} h^{-1} (mean 25.6 (SD 4.8) mg kg^{-1} h^{-1}).

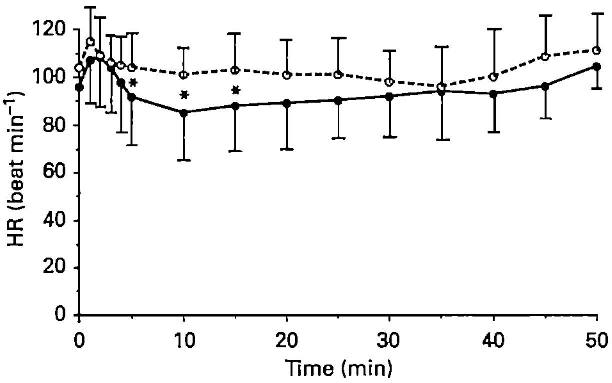


FIG. 1. Mean (SD) heart rates (HR) of patients in groups H (●) and P (○) at intervals after induction of anaesthesia. Time 0 = pre-induction reading. *$P < 0.05$ for difference between means.

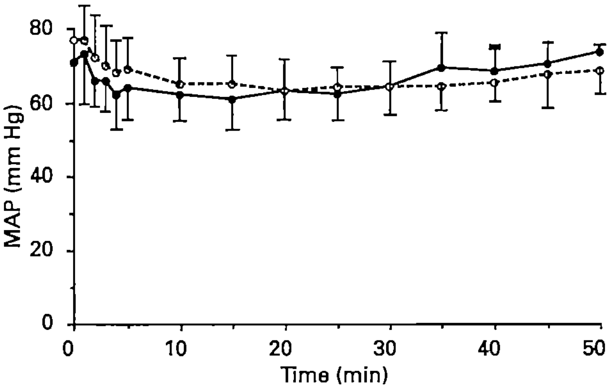


FIG. 2. Mean (SD) mean arterial pressures (MAP) of patients in groups H (●) and P (○) at intervals after induction of anaesthesia. Time 0 = pre-induction reading.

Two patients (10 %) in group H and four (20 %) in group P experienced pain or discomfort during induction of anaesthesia with propofol. Six (30 %) of patients in group H and five (25 %) in group P were apnoeic for 15–60 s after induction of anaesthesia. Involuntary movements occurred for a few seconds after induction of anaesthesia in five (25 %) patients in group H and three (15 %) patients in group P.

All patients were judged to be anaesthetized adequately and operating conditions were good in all cases. The mean heart rates in group P tended to be slightly faster than those in group H and the difference was just significant at the 5 % level on three occasions (5, 10 and 15 min) (fig. 1).

There was no significant difference in arterial pressure between the two groups at any time (fig. 2), and no significant difference in mean end-expired carbon dioxide concentration between them except at 15 min (fig. 3).

There was no significant difference between the groups in the time taken to spontaneous eye opening after discontinuation of the maintenance anaesthetic (10.5 min (range 3–32 min) in group H; 13.5 min (range 4–36 min) in group P). The calculated blood concentration of propofol at which patients in group P awoke was in the range 0.3–2.6 μg ml^{-1} (mean 1.4 μg ml^{-1}).

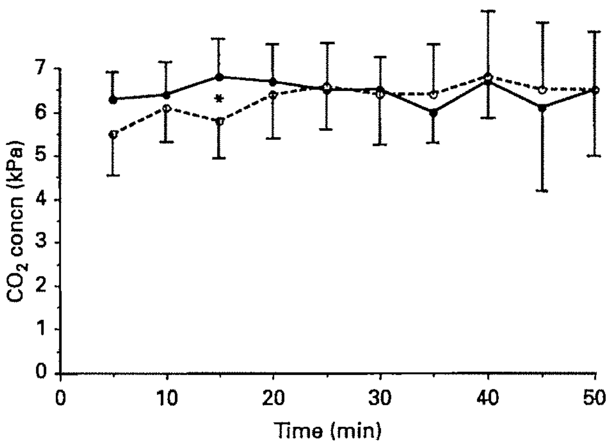


FIG. 3. Mean (SD) end-tidal carbon dioxide concentration of patients in groups H (●) and P (○) at intervals after induction of anaesthesia. *$P < 0.05$ for difference between means.

One patient in group H and two patients in group P complained of pain at the operative site and were treated with diclofenac sodium 1 mg kg^{-1} as required. All other patients were comfortable on recovery from anaesthesia.

DISCUSSION

More rapid recovery occurs after induction of anaesthesia with propofol compared with thiopentone in both children [5, 6] and adults. In these previous studies, anaesthesia was maintained with a volatile anaesthetic agent. The use of propofol as the induction agent for paediatric general surgery day-cases has been shown to produce earlier recovery from anaesthesia in all patients and earlier discharge in children aged more than 5 yr, although not in those younger than 5 yr [5].

Our study was designed to see if maintaining anaesthesia with an infusion of propofol rather than a volatile agent would produce larger differences in recovery times than the relatively small differences seen between children in whom anaesthesia was induced with propofol and those given thiopentone. The numbers of patients in the two groups were calculated to give the study a 95% chance of detecting a difference in recovery times that would be significant at the 5% level if differences in recovery times of the same magnitude as in other paediatric studies occurred [6–8].

There was a preponderance of boys in our study because paediatric day-case surgery tends to include a number of exclusively male conditions such as circumcision and orchidopexy. The differing numbers of particular regional blocks in groups H and P were a reflection of the normal practice of different consultant anaesthetists in performing regional blocks for circumcision, orchidopexy and inguinal hernia repair. Caudal anaesthesia and ilioinguinal nerve block have been shown to be equally effective and longlasting when used for orchidopexy and inguinal hernia surgery [11]. Caudal block and dorsal nerve block of the penis have been shown to have similar effectiveness and duration of analgesia when used for circumcision [12, 13]. We wished to reflect normal practice in day-case surgery during the study and, for this reason and given that the caudal, ilioinguinal nerve and dorsal nerve of penis blocks are equivalent when used appropriately, we did not standardize the regional blocks, which were performed by a registrar or senior registrar under the supervision of a consultant. Again, this was to reflect normal clinical practice in a teaching hospital. The fact that almost all patients (19 of 20 in group H and 18 of 20 in group P) were comfortable in the recovery room suggests that the blocks were generally effective and appropriate.

We found that the two groups were similar in all respects. Induction of anaesthesia was satisfactory in both groups, with a low incidence of minor side effects. Maintenance of anaesthesia was straightforward in both groups and operating conditions satisfactory.

Spontaneous eye opening has been shown [8] to be a sensitive indicator of recovery from general anaesthesia in children; there was no significant difference between the groups in the time from discontinuation of anaesthesia to spontaneous eye opening. This finding contrasts with a study of maintenance of anaesthesia by halothane or propofol in paediatric dental outpatients [8] in which significantly earlier recovery occurred in the propofol group. In that study, the mean duration of anaesthesia was 8.1 min in the thiopentone group and 6.3 min in the propofol group, compared with 30.6 min in group H and 33.3 min in group P in our study. The cumulative effects of anaesthetic agents during longer procedures may abolish the differences observed after short procedures [4]. The use of a regional block in our patients may also have reduced any tendency to quick recovery by reducing or eliminating postoperative pain.

Borgeat and colleagues [7] compared a thiopentone–halothane technique with a propofol induction and maintenance technique for E.N.T. procedures. Their patients were paralysed and no regional block was performed. The mean durations of surgery were 35 min (thiopentone–halothane) and 37 min (propofol) and there were significantly quicker times to tracheal extubation in the propofol group.

The lack of any significant cardiovascular or respiratory differences between the groups in our study is in agreement with that of Borgeat and colleagues [7]. This indicates that maintenance of anaesthesia by means of a target-controlled infusion of propofol in children breathing spontaneously without an opioid is not unduly depressant to the cardiovascular or respiratory systems.

REFERENCES

1. Rolly G, Versichelen L. Comparison of propofol and thiopentone for induction of anaesthesia in premedicated patients. *Anaesthesia* 1985; 40: 945–948.
2. Herbert M, Makin SW, Bourke JB, Hart EA. Recovery of mental abilities following general anaesthesia induced by propofol ("Diprivan") or thiopentone. *Postgraduate Medical Journal* 1985; 61 (Suppl. 3): 132.
3. Grant IS, MacKenzie N. Recovery following propofol ("Diprivan") anaesthesia—a review of three different anaesthetic techniques. *Postgraduate Medical Journal* 1985; 61 (Suppl. 3): 133–137.

4. Sanders LD, Isaac PA, Yeomans WA, Clyburn PA, Rosen M, Robinson JO. Propofol induced anaesthesia. *Anaesthesia* 1989; **44**: 200–204.
5. Runcie CJ, MacKenzie SJ, Arthur DS, Morton NS. Comparison of recovery from anaesthesia induced in children with either propofol or thiopentone. *British Journal of Anaesthesia* 1993; **70**: 192–195.
6. Mirakhur RK. Induction characteristics of propofol in children: comparison with thiopentone. *Anaesthesia* 1988; **43**: 593–598.
7. Borgeat A, Popovic V, Meier D, Schwander D. Comparison of propofol and thiopental/halothane for short duration E.N.T. surgical procedures in children. *Anesthesia and Analgesia* 1990; **71**: 511–515.
8. Puttick N, Rosen M. Propofol induction and maintenance with nitrous oxide in paediatric outpatient dental anaesthesia. *Anaesthesia* 1988; **43**: 646–649.
9. White M, Kenny GNC. Intravenous propofol anaesthesia using a computerised infusion system. *Anaesthesia* 1990; **45**: 204–209.
10. Marsh B, White M, Morton NS, Kenny GNC. Pharmacokinetic model driven infusion of propofol in children. *British Journal of Anaesthesia* 1991; **67**: 41–48.
11. Markham SJ, Tomlinson J, Hain WR. Ilioinguinal nerve block in children. A comparison with caudal blockade for intra and postoperative analgesia. *Anaesthesia* 1986; **41**: 1098–1103.
12. Vater M, Wandless J. Caudal or dorsal nerve block? A comparison of two local anaesthetic techniques for postoperative analgesia following day case circumcision. *Acta Anaesthesiologica Scandinavica* 1985; **29**: 175–179.
13. Yeoman PM, Cooke R, Hain WR. Penile block for circumcision? A comparison with caudal blockade. *Anaesthesia* 1983; **36**: 862–866.

British Journal of Anaesthesia 1993; 70: 546–551

PHARMACOKINETICS OF PROPOFOL ADMINISTERED BY INFUSION IN DOGS UNDERGOING SURGERY

A. NOLAN AND J. REID

SUMMARY

*We have investigated the pharmacokinetics of propofol in seven beagle dogs undergoing surgery for implantation of s.c. tissue pouches. Blood concentrations of propofol were measured using high pressure liquid chromatography with fluorescence detection. After premedication with acepromazine and papaveretum and induction of anaesthesia with propofol 4 mg kg^{-1} i.v., anaesthesia was maintained with propofol 0.4 mg kg^{-1} min^{-1} and 67% nitrous oxide in six dogs. In the seventh dog, the infusion rate was increased to 0.6 mg kg^{-1} min^{-1} in order to achieve surgical anaesthesia. The mean elimination half-life was 322.3 (sem 27.0) min, mean volume of distribution at steady state 6.510 (0.524) litre kg^{-1}, mean body clearance 50.1 (3.9) ml kg^{-1} min^{-1} and mean residence time 131.6 (8.9) min. The blood propofol concentrations achieved using this standard dosing regimen showed wide variation among individuals. All dogs recovered rapidly from anaesthesia. The mean time to extubation was 7.6 min and to standing unaided was 30.7 min from the end of the infusion. (*Br. J. Anaesth. 1993; **70**: 546–551)

KEY WORDS
Anaesthetics, intravenous: propofol.

We have previously reported the pharmacokinetics of propofol in the dog, which remains a popular model in medical research, despite a tendency to favour small laboratory animals for experimental purposes. When propofol is administered as either a single bolus or as a bolus before maintenance of anaesthesia with halothane, body clearance was greater in dogs than in man, elimination half-life was shorter and recovery from anaesthesia equally rapid [1]. However, the sampling period in that study was relatively short (6 h). Campbell and colleagues [2] have suggested that, when blood samples are collected over a relatively short period of time, this apparently rapid elimination may be misleading. These and other workers have reported longer elimination half-lives and lower clearance values which suggested that elimination of propofol from the body was relatively slower than reported previously [2–5]. This could be significant when propofol is used by infusion for the maintenance of anaesthesia in long surgical procedures. Albanese and colleagues [6] reported a mean elimination half-life of 1878 min and an increased clearance value in patients undergoing long-term infusions, but in this study there was considerable interpatient variation.

Consequently, we decided to investigate the pharmacokinetics of propofol infusion in dogs undergoing identical body surface surgery, in order to identify the blood concentrations required to maintain surgical anaesthesia and to define pharmacokinetic parameters using a longer sampling regimen. The work was carried out under Home Office Licence PPL 60/01048.

METHODS

Phamacokinetic studies in dogs given a single bolus dose of propofol have been carried out [1] and the mean results for volume of the central compartment (Vc) and body clearance (Cl) were used to estimate a loading dose (Xd) and infusion rate for this study as follows: $X\text{d} = C^{ss}.Vc$, where C^{ss} is the target concentration at steady state and infusion rate $= Cl.C^{ss}$. On the basis of a pilot infusion study carried out in bitches undergoing ovarohysterectomy, the target range for C^{ss} was set at 5–7 µg ml^{-1}.

We studied seven beagle dogs (three male) aged 8–9 months, weights 16–26.5 kg and free from clinical signs of disease. They were to be anaesthetized for implantation of four s.c. tissue cages in the flank region. Before anaesthesia, routine biochemical and haematological screening was carried out on each dog.

Food was withheld for all animals for 12–16 h, but water was freely available until 3 h before induction of anaesthesia. All dogs were premedicated with acepromazine maleate (ACP; CVet) 0.05 mg kg^{-1} and papaveretum (Omnopon; Roche) 0.4 mg kg^{-1}, given together i.m. 30 min before induction of anaesthesia. Propofol (Rapinovet; Pitman Moore) 4 mg kg^{-1} was injected as a bolus via a preplaced cannula located in the right cephalic vein. After tracheal intubation, the dogs were allowed to breathe spontaneously a mixture of 67% nitrous oxide in

---

Andrea Nolan, m.v.b., m.r.c.v.s., d.v.a., ph.d. (Department of Veterinary Pharmacology); Jacqueline Reid, b.v.m.s., m.r.c.v.s., d.v.a., ph.d. (Department of Veterinary Surgery); University of Glasgow, Bearsden Road, Bearsden, Glasgow G61 1QH. Accepted for Publication: November 24, 1992.

oxygen via a Magill non-rebreathing system with a fresh gas flow rate of 200 ml kg^{-1} min^{-1}.

One minute after induction, a zero order i.v. infusion of propofol 0.4 mg kg^{-1} min was begun using a volumetric infusion pump (Flo-Gard 6200; Baxter) and continued for 60 min. If anaesthesia was inadequate, the infusion rate was increased until the desired plane of anaesthesia was achieved. In all animals, the non-steroidal antiinflammatory drug flunixin meglumine (Finadyne; Schering Plough Animal Health) 1 mg kg^{-1} was injected s.c. 2 h after the infusion was terminated.

Venous blood samples (1.5 ml) were collected from a cannula located in the left cephalic vein, immediately before and during the infusion, and after it was terminated. Times of collection during the infusion were 2, 5, 10, 15, 20, 40 and 60 min. After the infusion was stopped, samples were taken at 2, 5, 10, 20, 30, 45, 60 min and then at 2, 3, 4, 6, 9, 20 and 24 h. Samples, collected in tubes containing potassium oxalate, were cooled immediately and stored at 4 °C until analysis. All samples were assayed within 2 weeks of collection and previous investigations have shown that blood stored in this way retains in excess of 98 % of its original propofol concentration. Whole blood concentrations of propofol were measured by high pressure liquid chromatography with fluorescence detection [7]. The limit of detection was approximately 5 ng ml^{-1} and the intra-assay coefficient of variation was 2.9 %.

Routine monitoring was carried out during anaesthesia. Heart rate and ventilatory frequency, systemic arterial pressure, end-tidal partial pressure of carbon dioxide ($P\text{E}'_{CO_2}$) and oxygen saturation were measured at 5-min intervals. Arterial pressure was monitored using a Dinamap pressure monitor (Critikon Canada Inc.) with an appropriately sized cuff placed over the middle coccygeal artery. $P\text{E}'_{CO_2}$ was monitored on a breath-by-breath basis using a carbon dioxide analyser (Normocap; Datex). Oxygen saturation was measured using a pulse oximeter (Ohmeda) located on the tongue.

Recovery times (tracheal extubation, head lift, sternal recumbency and standing unaided) were measured from the time the infusion was switched off. The blood concentration of propofol at the time of tracheal extubation and head-lift was calculated retrospectively by extrapolation from each individual propofol concentration–time curve.

The apparent elimination half-life, $T_{\frac{1}{2}}^{\beta}$ was calculated from the terminal log-linear portion of the post-infusion decay curve of blood concentration of propofol *vs* time, using the curve stripping programme CSTRIP [8]. The non-compartmental pharmacokinetic parameters, volume of distribution at steady state (V^{ss}), clearance (Cl) and mean residence time (MRT) were calculated according to standard methods using the statistical moment theory [9]. Area under the blood concentration (tC_P)–time (t) plots to infinity (AUC), and the area under the first moment curve (AUMC = $tC_P \times t^2$) were calculated from the first to the last blood propofol sample using the trapezoidal rule. An estimate of the infinite part of the curve was obtained from $t'C_P/\beta$, where t' = last measured blood concentration of propofol and β = overall elimination rate constant. An estimate of the infinite part of the AUMC plot was obtained from $t'C_P \times t'/\beta$. MRT corrected for infusion duration, was calculated from AUC and AUMC (MRT = AUMC/AUC − T/2) where T is the infusion time. V^{ss} was calculated from $Cl \times$ MRT [10].

RESULTS

Six of the seven dogs had a constant rate infusion, while the seventh required two increases in infusion rate. Consequently, results for blood propofol concentrations are expressed as a mean for six animals (dogs Nos 1–6). Blood concentrations of propofol varied between 3.77 and 5.52 µg ml^{-1} as the infusion was started. A mean concentration of 5 µg ml^{-1} (range 3.34–6.60 µg ml^{-1}) was achieved within 10 min, indicating a rapid approach towards the target concentration range, although the between-animal variation was large. The propofol concentration increased gradually over the next 50 min until the infusion was switched off, at which point the mean concentration was 5.84 (SEM 0.54) µg ml^{-1} (range 4.0–7.1 µg ml^{-1}) (fig. 1A). In dogs Nos 1–6, surgery began within 15 min of the start of the infusion, at which time the blood concentrations of propofol were in the range 3.5–5.8 µg ml^{-1}. After cessation of the infusion, the blood concentration of propofol declined in a polyexponential manner (fig. 1B). Measurable blood concentrations of propofol were present in all dogs for 25 h.

Tracheal intubation was not possible immediately after induction in dog No. 7, and after 10 min the infusion rate was increased to 0.5 mg kg^{-1} min^{-1}. Four minutes later, the infusion rate was increased again to 0.6 mg kg^{-1} min^{-1} in order to achieve surgical anaesthesia. At 15 min, this animal had a blood concentration of propofol 5.4 µg ml^{-1} and intubation was successful. When surgery began 20 min after the start of the infusion, the blood concentration of propofol was 5.82 µg ml^{-1}. The rate of infusion was reduced to 0.5 mg kg^{-1} min^{-1} after 40 min and again 6 min later to 0.4 mg kg^{-1} min^{-1}. At the end of the infusion period the blood concentration of propofol was 7.9 µg ml^{-1}. During surgery, although no movement was recorded and cardiovascular variables remained stable, an increase in ventilatory frequency was evident as s.c. tunnelling was performed.

Clinically, all animals were in a light plane of anaesthesia. A brisk palpebral reflex was present for the first 30–40 min of the infusion in five dogs and on occasions spontaneous blinking was noted.

The mean elimination half-life for all seven dogs was 322.3 (27.0) min, mean clearance 50.1 (3.9) ml kg^{-1} min^{-1}, V^{ss} 6.510 (0.524) litre kg^{-1} and MRT 131.6 (8.9) min. The pharmacokinetic variables for each dog are shown in table I.

Mean values for physiological parameters are shown for six dogs, omitting dog No. 7 which received a greater total dose of propofol than the other six animals. Systolic arterial pressure decreased from 130 (5) mm Hg 5 min before induction to a smallest value of 111 (3) mm Hg 5 min after

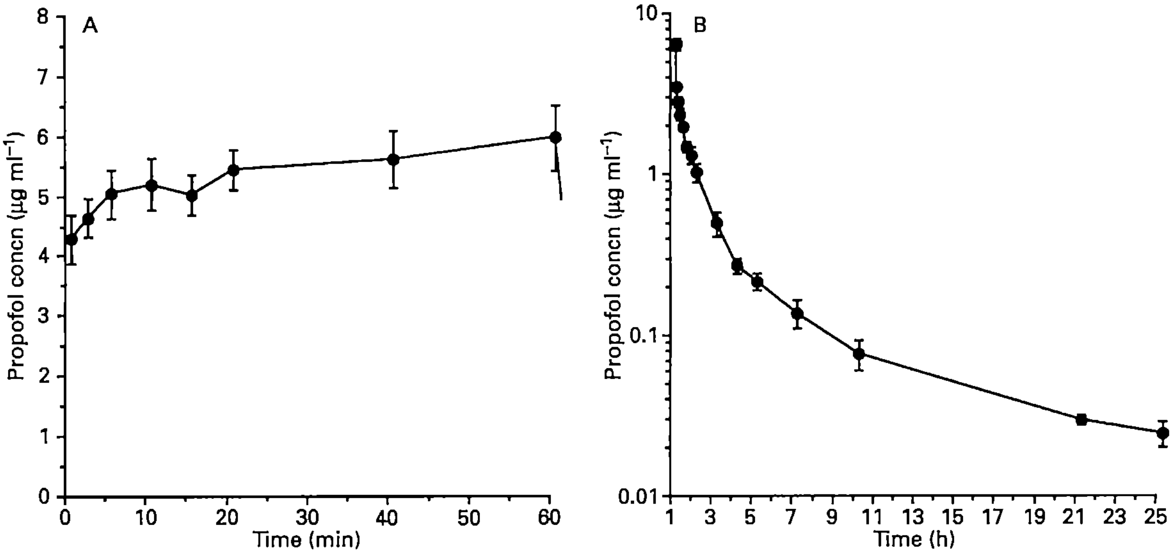


FIG. 1. A: Blood concentration of propofol achieved during a 60-min infusion period in six dogs (mean, SEM). B: Semilogarithmic plot of mean blood concentrations of propofol against time after a 1-h propofol infusion (mean, SEM of six dogs).

TABLE I. *Pharmacokinetic variables for each dog given propofol 4 mg kg^{-1} for induction of anaesthesia and maintained with propofol 0.4 mg kg^{-1} min^{-1} for 1 h. MRT = Mean residence time*

Dog No.	Clearance (ml kg^{-1} min^{-1})	Vd^{ss} (litre kg^{-1})	Elimination half-life (min)	MRT (min)
1	41.3	6.319	307.7	153.0
2	53.8	8.522	337.2	158.4
3	41.8	5.543	285.6	132.6
4	41.4	5.912	458.8	142.8
5	54.2	5.236	324.8	96.6
6	67.2	8.104	289.3	120.6
7	50.7	5.932	252.7	117.0
Mean	50.1	6.510	322.3	131.6
SEM	3.9	0.524	27.0	8.9

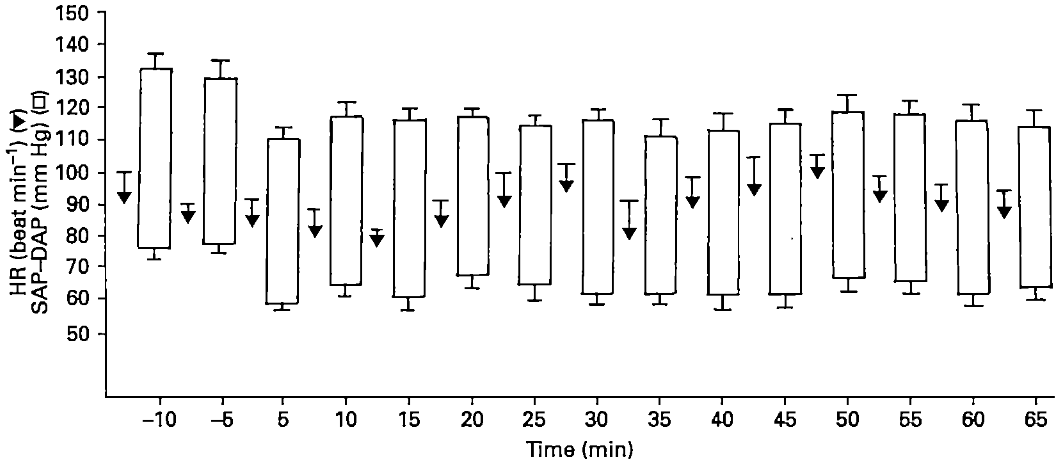


FIG. 2. Changes in systolic and diastolic arterial pressures (☐) and heart rate (▼) during a 60-min propofol infusion (mean, SEM of six dogs).

induction (fig. 2). Thereafter, it remained relatively stable, varying between 112 and 121 mm Hg. The diastolic pressure followed a similar pattern (fig. 2) with a maximum decrease of 20% recorded 5 min after induction. During anaesthesia, the heart rate varied minimally from a preinduction value of 85 beat min^{-1} (fig. 2). Post-induction apnoea was recorded in one dog, spontaneous ventilation returning after 3 min. $P\text{E}'_{CO_2}$ values increased from a mean value of 5.9 (0.4) kPa 5 min after induction to 6.7 (0.3) kPa, while ventilatory frequency remained largely unchanged from preinduction values (fig. 3).

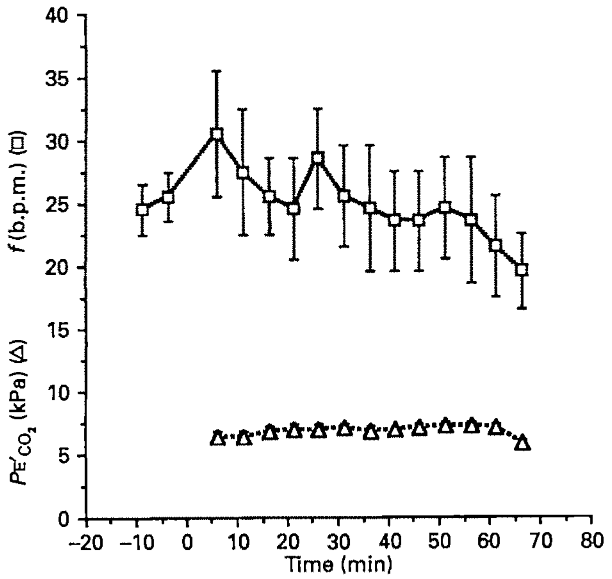


FIG. 3. Changes in ventilatory frequency (*f*) (□) and end-tidal partial pressure of carbon dioxide ($P_{E'CO_2}$) (△) tension during a 60-min propofol infusion (mean, SEM of six dogs).

TABLE II. *Recovery times measured from the end of a 1-h infusion of propofol 0.4 mg kg^{-1} min^{-1}*

Dog No.	Extubation (min)	Head-lift (min)	Sternal recumbency (min)	Standing unaided (min)
1	8	14	55	69
2	4	4	14	18
3	6	8	13	32
4	6	13	19	40
5	10	12	18	23
6	11	13	17	18
7	8	9	10	25
Mean	7.6	10.4	20.8	30.7
SEM	1.0	1.5	6.3	8.0

Oxygen saturation was not measured before induction of anaesthesia, but remained greater than 90 % throughout the course of anaesthesia.

Recovery from anaesthesia was rapid in all dogs (table II). One dog remained in lateral recumbency for 55 min, but appeared fully conscious. The mean blood concentration of propofol at extubation was 2.3 μg ml^{-1} (range 2.1–2.9 μg ml^{-1}) and at head lift 2.1 μg ml^{-1} (range 1.7–2.7 μg ml^{-1}).

DISCUSSION

The combination of a bolus dose followed by a relatively rapid infusion of propofol allowed us to achieve surgical anaesthesia within 20 min in all dogs. Respiratory depression was evident throughout anaesthesia, but was considered acceptable in this group of spontaneously breathing dogs. $P_{E'CO_2}$ had returned to a mean of 5.3 kPa within 5 min of the end of the infusion, indicating that there was little respiratory depression persisting into the recovery period.

Arterial hypotension occurs commonly during induction of anaesthesia with a bolus injection of propofol, and this has been attributed to a decrease in systemic vascular resistance [11–13]. However, more recently Puttick and colleagues [14] have demonstrated that reduction in preload and myocardial contracility contributed to propofol-induced hypotension in a group of open chested dogs. In the present study, the greatest changes in systolic and diastolic arterial pressures were recorded 5 min after induction of anaesthesia. However, these dogs had received acepromazine, a phenothiazine tranquillizer, as part of the premedicant 30 min before the induction of anaesthesia. In addition to its tranquillizing properties, this drug causes moderate hypotension in the dog as a result of peripheral vasodilatation [15], which would contribute to the hypotension recorded during induction and maintenance of anaesthesia.

Previous studies of propofol in humans and experimental animals have shown that individual variations in blood concentrations of propofol may occur [14, 16]. Similarly, in the present study, marked variation in blood concentrations of propofol occurred, despite the identical infusion rate. Such variation was not reflected clinically, however, as six dogs appeared to be in a similar anaesthetic plane. The exception was dog No. 7: the trachea could not be intubated until the blood concentration of propofol reached 5.4 μg ml^{-1}.

In man, there seems to be wide variation in blood concentrations of propofol associated with the abolition of response to surgical stimulus, with the concurrent use of other drugs making comparisons difficult [17–19]. Turtle and others reported that a propofol concentration of 5.9 μg ml^{-1} abolished movement to skin incision in 95 % of patients who had received lorazepam as a premedicant [20]. This value is similar to that found in our dogs, which had been sedated with a neuroleptanalgesic mixture. However, the additional analgesic activity of this mixture must be set against the substantially lower efficacy of nitrous oxide in dogs [21] compared with man.

Gepts and co-workers [22] administered propofol to patients by continuous infusion at a maximum rate of 0.15 mg kg^{-1} min^{-1} and found that there was an initial increase in blood concentration over 10 min, followed by a slower rate of increase over the infusion period. After the infusion they measured a long third phase (355 min), which they suggested was unlikely to play a significant role in the rate of recovery of consciousness because blood concentrations were so small. In our canine study, blood concentrations of propofol followed a similar pattern, but we consider that a zero order infusion of this magnitude (0.4 mg kg^{-1} min^{-1}), if maintained for long periods, could result in delayed recovery from anaesthesia because of cumulation of propofol in tissue stores. Limited clinical experience of prolonged infusion of propofol to dogs supports this view [23].

During the post-infusion decay of propofol from blood, three of seven animals showed small secondary peaks, dogs Nos 1 and 2 at 240 min and dog No. 4 at 45 min, all of which were less than 20 % of the previous sample value. This is in contrast with infusion studies in man which have demonstrated occasional profound increases in blood concentration of propofol during the recovery period [5, 6, 18].

Previous studies in the dog have reported a $T_{\frac{1}{2}}^{\beta}$ of 90.9 min with a high clearance value of 58.6 ml kg^{-1} min^{-1} [1]. This clearance is in excess of liver blood flow [24] and lends weight to the argument for an extrahepatic site of metabolism. Morgan, Campbell and Crankshaw [3] suggested that, in humans, clearance values from single bolus studies were an overestimate of the true body clearance when applied to infusion studies, but we have shown that in the dog the mean clearance for propofol by infusion, 50.1 ml kg^{-1} min^{-1}, is similar to that found in single bolus studies. However, the elimination half-life was considerably greater than that calculated from single dose studies. This is probably a reflection of the fact that samples were collected over a much longer period of time. Similar findings have been demonstrated in patients undergoing long-term mechanical ventilation who received propofol by infusion [6] and other workers investigating the pharmacokinetics of propofol from infusion studies have reported a variety of prolonged half-lives of 13.1–44.7 h [3].

The volume of distribution was large, 6.5 litre kg^{-1}, confirming the extensive distribution of propofol from blood into tissues, and is not unexpected for such a highly lipophilic drug. These values are greater than those recorded in humans by some groups [18, 22, 25], but less than that reported by Albanese and coworkers [6].

Blood concentration of propofol at awakening has been measured in man and the evidence suggests that, when propofol is given by infusion, the range is 0.74–1.66 μg ml^{-1} [22]. In a study carried out in pregnant women, it was reported that patients who received a greater infusion rate during surgery opened their eyes at the same time (mean 6 min) as those that received a lesser infusion rate, although the blood concentrations of propofol were significantly greater (1.74 μg ml^{-1} *vs* 1.24 μg ml^{-1}) [26]. It is difficult to assess time of awakening in dogs. We regard the ability to maintain head-lift as the criterion for awakening in animals, although it may not be totally comparable to eye opening in man. The blood concentrations of propofol at awakening obtained in these dogs, greater than recorded in humans and from dogs given a single bolus dose of propofol [1], probably reflect the greater infusion rate used in this study, but the recovery times compare favourably.

In conclusion, we have shown that although the elimination half-life of propofol in dogs was considerably longer than that recorded from single bolus dose studies, body clearance was high. In addition, there was considerable between-animal variation in blood concentrations of propofol measured during a zero order infusion and in blood concentrations required to maintain anaesthesia for body surface surgery.

ACKNOWLEDGEMENTS

We thank Peter Baxter for this technical assistance and ICI for donation of pure propofol.

REFERENCES

1. Nolan AM, Reid J, Grant S. The effect of halothane and nitrous oxide on the pharmacokinetics of propofol in dogs. *Journal of Veterinary Pharmacology and Therapeutics* 1992; (in press).
2. Campbell GA, Morgan DJ, Kumar K, Crankshaw DP. Extended blood collection period required to define distribution and elimination kinetics of propofol. *British Journal of Clinical Pharmacology* 1988; **26**: 187–190.
3. Morgan DJ, Campbell GA, Crankshaw DP. Pharmacokinetics of propofol given by intravenous infusion. *British Journal of Clinical Pharmacology* 1990; **30**: 144–148.
4. Cockshott ID, Briggs LP, Douglas EJ, White M. Pharmacokinetics of propofol in female patients. Studies using single bolus injections. *British Journal of Anaesthesia* 1987; **59**: 1103–1110.
5. Kay NH, Sear JW, Uppington J, Cockshott ID, Douglas EJ. Disposition of propofol in patients undergoing surgery. A comparison in men and women. *British Journal of Anaesthesia* 1986; **58**: 1075–1079.
6. Albanese J, Martin C, Lacarelle B, Saux P, Duraind A, Gouin F. Pharmacokinetics of long-term propofol infusion used for sedation in ICU patients. *Anesthesiology* 1990; **73**: 214–217.
7. Plummer GF. Improved method for the determination of propofol in blood by high performance liquid chromatography with fluorescence detection. *Journal of Chromatography* 1987; **421**: 171–176.
8. Sedman AJ, Wagner JG. CSTRIP, a Fortran IV computer programme for obtaining initial polyexponential parameter estimates. *Journal of Pharmaceutical Sciences* 1976; **65**: 1006–1010.
9. Gibaldi M. *Biopharmaceutics and Clinical Pharmacokinetics*, 3rd Edn. Philadelphia: Lea and Febiger, 1984.
10. Veng-Pedersen P. Mean time parameters in pharmacokinetics. Definition, computation and clinical implications (part 1). *Clinical Pharmacokinetics* 1989; **17**: 345–366.
11. Grounds RM, Twigley AJ, Carli F, Whitwam JG, Morgan M. The haemodynamic effects of intravenous induction. Comparison of the effects of thiopentone and propofol. *Anaesthesia* 1985; **40**: 735–740.
12. Claeys MA, Gepts E, Camu F. Haemodynamic changes during anaesthesia induced and maintained with propofol. *British Journal of Anaesthesia* 1988; **60**: 3–9.
13. Goodchild CS, Serrao JM. Cardiovascular effects of propofol in the anaesthesized dog. *British Journal of Anaesthesia* 1989; **63**: 87–92.
14. Puttick RM. Diedericks J, Sear JW, Glen JB, Foëx P, Ryder WA. Effect of graded infusion rates of propofol on regional and global left ventricular function in the dog. *British Journal of Anaesthesia* 1992; **69**: 375–381.
15. Turner DM, Ilkiw JE, Rose RJ, Warren JM. Respiratory and cardiovascular effects of five drugs used as sedatives in the dog. *Australian Veterinary Journal* 1974; **50**: 260–265.
16. Schuttler J, Kloos S, Schwilden H, Stoeckel H. Total intravenous anaesthesia with propofol and alfentanil by computer assisted infusion. *Anaesthesia* 1988; **43** (Suppl): 2–7.
17. Dixon J, Roberts FL, Tackley RM, Lewis GTR, Connell H, Prys-Roberts C. Study of the possible interaction between fentanyl and propofol using a computer-controlled infusion of propofol. *British Journal of Anaesthesia* 1990; **64**: 142–147.
18. Schafer A, Doze VA, Shafer SL, White PF. Pharmacokinetics and pharmacodynamics of propofol infusions during general anesthesia. *Anesthesiology* 1988; **69**: 348–356.
19. Spelina KR, Coates DP, Monk CR, Prys-Roberts C, Norley I, Turtle MJ. Dose requirements of propofol by infusion during nitrous oxide anaesthesia in man. 1: patients premedicated with morphine. *British Journal of Anaesthesia* 1986; **58**: 1080–1084.
20. Turtle MJ, Cullen P, Prys-Roberts C, Coates D, Monk CR, Faroqui MH. Dose requirements of propofol by infusion during nitrous oxide anaesthesia in man. 2: patients premedicated with lorazepam. *British Journal of Anaesthesia* 1987; **59**: 283–287.
21. Steffey EP, Gillespie JR, Berry JD, Eger EI, Munson ES. Anesthetic potency (MAC) of nitrous oxide in the dog, cat

and stump-tail monkey. *Journal of Applied Physiology* 1974; **36**: 530–532.
22. Gepts E, Carmu F, Cockshott ID, Douglas EJ. Disposition of propofol administered as constant rate intravenous infusions in humans. *Anesthesia and Analgesia* 1987; **66**: 1256–1263.
23. Reid J, Nolan AM. Prolonged recovery following propofol infusion in a dog: a case report. *Journal of Veterinary Anaesthesia* 1992; **19**: 61–64.
24. Juhl B, Einer-Jensen N. Hepatic blood flow and cardiac output during halothane anaesthesia: an animal study. *Acta Anaesthesiologica Scandinavica* 1974; **18**: 114–122.
25. Cockshott ID, Douglas EJ, Prys-Roberts C, Turtle M, Coates DP. The pharmacokinetics of propofol during and after intravenous infusion in man. *European Journal of Anaesthesiology* 1990; **7**: 265–275.
26. Gin T, Yau G, Chan K, Gregory MA, Oh TE. Disposition of propofol infusions for Caesarean section. *Canadian Journal of Anaesthesia* 1991; **38**: 31–36.

British Journal of Anaesthesia 1993; 70: 552–555

IN VIVO DETERMINATION OF CONCENTRATION–EFFECT CURVES OF LOCAL ANAESTHETICS IN MAN

R. WIESEMES, W. KLEMENT, G. E. K. NOVOTNY AND P. LIPFERT

SUMMARY

In clinical use, the concentrations of local anaesthetics at the site of action are unknown. With the method described here, concentrations of local anaesthetics can be predetermined and kept constant at the site of action. In six volunteers, a blister was raised on the ventral surface of the forearm. After removal of the epithelium, the blister base was rinsed continuously with carbogenated Tyrode's solution with and without increasing concentrations of bupivacaine (Carbostesin) for 15 min each. The effects of bupivacaine were determined by changes in the perception (tactile sensation) of drops falling on the blister base from increasing heights. The minimal height at which the drops were just perceived characterized the threshold of perception. With increasing bupivacaine concentrations, threshold increased until the drops were no longer perceived, at a median concentration of 2.48 mmol litre^{-1} (range 1.24–3.10 mmol litre^{-1}). After the blister base was rinsed with Tyrode's solution, threshold of perception reached baseline values, which was in accordance with an intact blister base. (Br. J. Anaesth. 1993; **70**: 552–555)

KEY WORDS

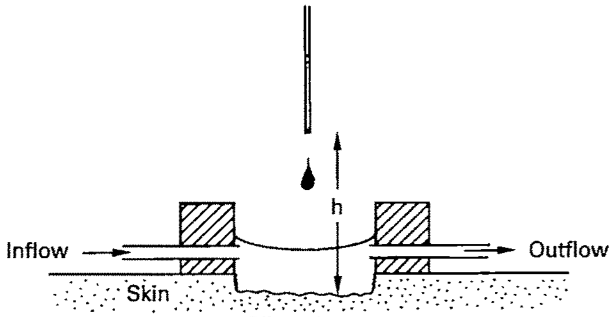
Anaesthetics, local. Pharmacodynamics: threshold concentration.

The concentrations of local anaesthetics at the site of action are unknown in clinical use [1]. Thus concentration–effect curves have been derived exclusively in animals by dissecting and bathing isolated nerves [2]. The present experiments aimed to develop a simple method in man by which concentrations of local anaesthetics could be predetermined and kept constant at the site of action. The method described here fulfilled these criteria and allowed us to test the sensitivity of neural

[redacted]

blister base was uncovered under sterile conditions, it was sealed in an open chamber (fig. 1) and rinsed continuously with carbogenated Tyrode's solution (flow 1.5 ml min^{-1}) with and without increasing concentrations of bupivacaine (Carbostesin). The solutions used were warmed to keep the blister base temperature within ±2 °C of the surrounding skin temperature as measured by infra-red telethermometry. The pH of the solutions was 7.3–7.5. The effects of bupivacaine were determined by means of changes in the perception of drops of equal size falling on the blister base from increasing heights. The minimal height at which the drops were just perceived characterized the perception threshold and was quantified by a millimetre scale connected with a support. The perception threshold was evaluated by the method of limits [4, 5]—that is, as the mean intensity of the last stimulus less than and the first greater than threshold.

After the blister base had been rinsed continuously with Tyrode's solution for 15 min, the perception threshold was evaluated in each volunteer (baseline). For this purpose, drops of the same composition were released on the blister base from increasing heights. The volunteers were asked to report if the drops touching the blister base were perceived or not. In the same way, the effect of each drug concentration was determined.



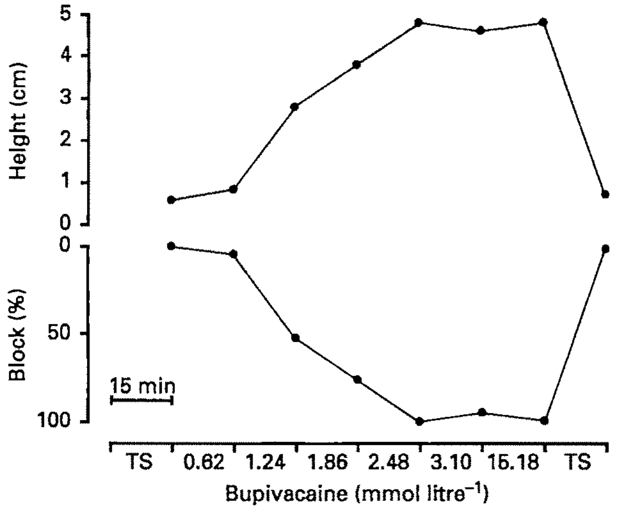


FIG. 2. A typical experimental programme. Bupivacaine concentrations were increased by 0.62 mmol and the corresponding perception thresholds (release height) evaluated (upper graph). The local anaesthetic effect of each concentration was expressed by the percent changes of perception threshold, the baseline threshold (Tyrode's solution; 0.6 cm) being set arbitrarily at 0, the threshold at maximal blocking effect (4.5 cm) at 100. Thus the blocking effects are expressed in percent of the maximal effect (relative blocking effect) (lower graph).

Starting with the smallest bupivacaine concentration (0.62 mmol litre^{-1}), the concentrations were increased stepwise. Each concentration was maintained until perception threshold repeatedly remained constant, thus demonstrating an equilibrium between the concentration at the site of action with that of the bathing solution. As the local anaesthetic effect reached a plateau within 2 min after administration, periods of 15 min for each concentration seemed to be adequate. The smallest bupivacaine concentration above which threshold remained constant was defined as the minimal blocking concentration. This definition relies on the premise that drops released from greater heights would be perceived via mechanoreceptors outside the blister base. To compare the perception threshold at the end of the experiment with the baseline value, the blister base was rinsed with Tyrode's solution again.

In one volunteer a wedge-shaped piece of the blister base and the surrounding skin was excised. It was examined to see if the epithelium was disconnected from the underlying tissues. The material was fixed by immersion in 1.25% glutaraldehyde and 1% paraformaldehyde in phosphate buffer 0.1 mol litre^{-1} at pH 7.4. Dehydration was by passage through the ascending acetone series, and the block was embedded in Spurr's medium. Semithin sections were stained with toluidine-blue.

Data analysis

Each threshold was determined four times and mean values calculated. The local anaesthetic effect was expressed by relating the percent changes in perception threshold against drug concentrations, the baseline threshold (Tyrode's solution) being arbitrarily set at 0, the threshold at maximal blocking effect at 100.

RESULTS

The results of a typical experiment are illustrated in figure 2. While the blister base was rinsed with Tyrode's solution, drops released from a height above 0.6 cm were just perceived, so that the perception threshold was 0.6 cm (upper graph). Note that the perception threshold increased as the bupivacaine concentrations increased; that is, to evoke the same minimal perception the release height had to be increased. As the perception threshold (4.5 cm) did not change with large concentrations (15.18 mmol litre^{-1}), the smallest concentration with the same threshold was defined as minimal blocking concentration (2.48 mmol litre^{-1}). At the end of the experiment, the blister base was rinsed with Tyrode's solution again, the threshold of perception being identical with baseline (0.6 cm). By relating blocking concentration of bupivacaine (X-axis) against drug effect expressed as percent of maximal

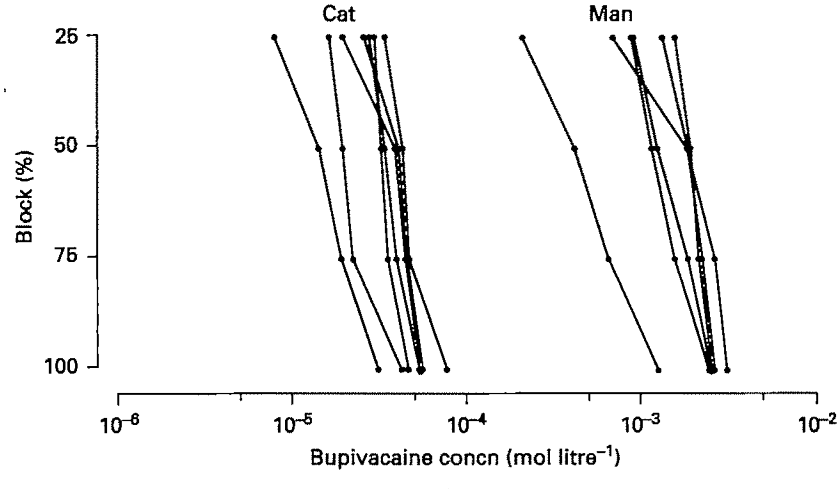


FIG. 3. Concentration–effect curves of bupivacaine derived from the blister base in man at pH 7.4 and normal skin temperature (right). The blocking concentrations for various degrees of blocking effect (75%, 50%, 25%) were interpolated, as in the experiments on the isolated aortic nerve of cats (pH 7.4, 38 °C [2]) depicted on the left for comparison. X-axis: blocking concentration (logarithmic scale); Y-axis: relative blocking effect (100 = threshold at maximal blocking effect). The concentration–effect curves are similar, but the blocking concentrations in the blister base are 45-fold greater than in the isolated nerve preparation.

effect (= relative blocking effect; *Y*-axis) a concentration–effect curve was plotted (lower graph). In each case, the drops were perceived as tactile sensation.

The individual concentration–effect curves derived from such experiments are illustrated in the right part of figure 3 (curves in the left part: see Discussion). In each experiment, the blocking effect increased in a concentration-dependent manner, the maximal blocking effects (minimal blocking concentrations) ranging from 1.24 to 3.10 mmol litre^{-1} (median 2.48 mmol litre^{-1}). For each drug concentration, a concentration equilibrium was established within 2 min. After the blister base was rinsed with Tyrode's solution, in each volunteer at the end of the experiments, perception threshold reached baseline values within 3 min. In five volunteers, the wound healed by primary intention and in one it healed by secondary intention with scar formation.

Histological examination of one blister periphery revealed that the cover of the blister consisted of epithelial layer exclusively, while the blister base was intact dermis.

DISCUSSION

The validity of our method rests on the assumption that the bupivacaine concentration in the bathing solution equals that at its site of action. Three observations support this assumption: (1) The diffusion distance between blister base and site of action was very small, as evident from anatomical and pharmacological findings. In the cantharides blister [6], the epithelium as a diffusion barrier was removed completely by uncovering the blister base. Thus mechanoreceptors sensing tactile stimuli, located at the tip of intermediate epithelial ridges and in the papillary ridges of the dermis [7, 8], are located within 100 µm from the blister base [7]. Also, the rapid establishment of plateau effects within 2–3 min (block and recovery from block, respectively) suggests diffusion distances less than 200 µm [1, 2]. That the blocking effect of bupivacaine was abolished within 3 min after the blister base was rinsed with Tyrode's solution is in accordance with earlier findings in isolated nerves [2]. The absence of an epithelial barrier and perineural binding structures may explain this rapid recovery. (2) Short diffusion distances guarantee concentration equilibrium only when more drug molecules are transported to the site of action than diffuse away. Even with maximal blood flow (8000 ml min^{-1}; [9]) in human skin (surface area 1.7 m^2), blood flow under the blister base (0.2 cm^2) is thought to be 0.1 ml min^{-1}, only a fraction of the 1.5 ml min^{-1} used in our experiments. Consequently, blister base and underlying tissues are provided with bupivacaine in abundance. (3) Although the maximal bupivacaine effect was reached within 2 (block)–3 (recovery) min, exposure time was 15 min to ensure drug equilibrium.

During generation of the blister, care was taken to keep the water temperature at 38–40 °C, as painful heat trauma should be avoided, which could sensitize and thus decrease the threshold of perception [10]. Absence of morphological damage and identical perception thresholds with Tyrode's solution before and after the blocking procedure suggest integrity of the blister base. In an effort to rank the results of the blister base method, we have compared our data with those determined in a "classical" manner—that is, in animals, by dissecting and bathing isolated nerves. As the information sensed by mechanoreceptors travels along A-fibres (conduction velocity 40–80 m s^{-1} [8]), blocking experiments in the aortic nerve of cats (A-fibres, mainly A-∂-fibres) were viewed for comparison. In these experiments [2], concentration–effect curves and minimal blocking concentrations (see left part of figure 3) were measured by bathing the nerve in increasing concentrations of bupivacaine (pH 7.4, 38 °C) and simultaneous recording of nerve activity. Surprisingly, the curves are similar in shape, and slope. Obviously, the same alterations in concentration induce the same alterations in effect characterizing similar drug–"receptor" interactions of the two preparations [11]. Also, interindividual variability does not differ, although one volunteer seemed to be conspicuously sensitive.

In contrast, however, the blocking concentrations derived from the present experiments were 45-fold greater than the minimal blocking concentrations in the aortic nerve of cats (fig. 3). Also, in experiments performed in isolated perfused vein segments of humans, the blocking concentrations were greater than in the isolated perfused nerve of the cat, by a factor of 30 [12]. There are two possible explanations for this difference:

(1) Axons are blocked, as probably occurs clinically. In this case, great blocking concentrations may be necessary because of short exposure lengths (less than three nodes of Ranvier). This assumption is based on recent experiments in isolated frog sciatic nerves [13], in which an inverse relation between blocking length and local anaesthetic concentration was found; that is, the smaller the exposure length, the greater the blocking concentration. As the nerves supplying the mechanoreceptors in the skin run perpendicularly up to the epithelium [7] and these receptors are located close to the blister base; the depth of local anaesthetic penetration into the dermis equals the exposure length of axons.

(2) Mechanoreceptors located close to the blister base and thus easily accessible for bupivacaine are blocked. As receptors are said to be less sensitive to local anaesthetics than nerve fibres (see figure 5 in [14]), they are blocked only with large concentrations. Receptor block does not seem to be involved in local anaesthesia under clinical circumstances.

ACKNOWLEDGEMENTS

The authors thank Prof. Dr J. O. Arndt, Department of Experimental Anaesthesiology, and Prof. Dr J. Tarnow, Department of Clinical Anaesthesiology.

REFERENCES

1. de Jong RH. *Local Anesthetics*, 2nd Edn. Springfield, Illinois: Charles C. Thomas, 1977.
2. Lipfert P, Seitz R, Arndt JO. Studies of local anesthetic action on natural spike activity in the aortic nerve of cats. *Anesthesiology* 1987; **66**: 210–213.

3. Keele CA, Armstrong D. *Substances Producing Pain and Itch.* London: Arnold, 1964.
4. Gescheider GA. *Psychophysics—Method and Theory*, 2nd Edn. Hillsdale, New Jersey: Erlbaum, 1976.
5. McBurney D, Collings V. *Introduction to Sensation/Perception*, 3rd Edn. Englewood Cliffs, New Jersey: Prentice-Hall, 1977.
6. Armstrong D, Dry RML, Keele CA, Markham JW. Observations on chemical excitants of cutaneous pain in man. *Journal of Physiology (London)* 1953; **120**: 326–351.
7. Darian-Smith I. The sense of touch: Performance and peripheral neural processes. In: Brookhart JM, Darian-Smith I, Geiger SR, Mountcastle V, eds. *Handbook of Physiology, Section 1: The Nervous System.* Bethesda, Maryland: American Physiological Society, 1984; 739–788.
8. Vallbo AB, Johansson RS. Properties of cutaneous mechanoreceptors in the human hand related to touch sensation. *Human Neurobiology* 1984; **3**: 3–14.
9. Rowell LB. *Human Circulation—Regulation During Physical Stress*, 1st Edn. New York, Oxford: Oxford University Press 1986.
10. Torebjörk HE, LaMotte RH, Robinson CJ. Peripheral neural correlates of magnitude of cutaneous pain and hyperalgesia: Simultaneous recordings in humans of sensory judgements of pain and evoked responses in nociceptors with c-fibers. *Journal of Neurophysiology* 1984; **51**: 325–339.
11. Ross EM, Gilman AG. Pharmacodynamics: Mechanisms of drug action and the relationship between drug concentration and effect. In: Gilman AG, Goodman LS, Rall TW, Murad F, eds. *Goodman and Gilman's The Pharmacological Basis of Therapeutics.* New York: Macmillan Publishing Company, 1985; 35–48.
12. Klement W, Arndt JO. Das isolierte Venensegment zur Bestimmung der pharmakologischen Eigenschaften von Lokalanaesthetika an Nozizeptoren des Menschen *in vivo. Anaesthesist* 1991; **40**: 562–563.
13. Raymond SA, Steffensen SC, Gugino LD, Strichartz GR. The role of length of nerve exposed to local anesthetics in impulse blocking action. *Anesthesia and Analgesia* 1989; **68**: 563–570.
14. Paintal AS. Effects of drugs on chemoreceptors, pulmonary and cardiovascular receptors. *Pharmacology and Therapeutics* 1977; **3**: 41–63.

British Journal of Anaesthesia 1993; 70: 556–561

I.V. BOLUS ADMINISTRATION OF SUBCONVULSIVE DOSES OF LIGNOCAINE TO CONSCIOUS SHEEP: RELATIONSHIPS BETWEEN MYOCARDIAL PHARMACOKINETICS AND PHARMACODYNAMICS

Y. F. HUANG, R. N. UPTON AND W. B. RUNCIMAN

SUMMARY

We have studied relationships between the time-courses of lignocaine concentrations in arterial and coronary sinus blood and myocardial tissue, and negative inotropic effects on the myocardium, after i.v. bolus administration of 50-, 75- or 100-mg doses of lignocaine to conscious, chronically instrumented sheep. Peak arterial and coronary sinus blood lignocaine concentrations occurred 26–38 s before and 29–78 s after the maximum decreases in myocardial contractility, respectively. Peak myocardial concentrations occurred simultaneously with the maximum decreases in myocardial contractility, except for the 100-mg doses. Anticlockwise hysteresis occurred only between arterial blood lignocaine concentrations and the negative inotropic effect. It was concluded that, after short-term i.v. administration, only the myocardial concentrations of lignocaine were in pseudoequilibrium with the negative inotropic effects of the lignocaine on the myocardium. (Br. J. Anaesth. 1993; **70**: 556–561)

KEY WORDS

Anaesthetics, local: lignocaine. Heart: myocardial drug concentration. Pharmacodynamics. Pharmacokinetics.

An assumption in many pharmacokinetic studies is that the drug concentrations in the "biophase" are proportional to, or in pseudoequilibrium with, blood drug concentrations, and that there is a simple relationship between this biophase concentration and the magnitude of the effects of the drug. While this may be true after the long-term use of drugs, in the first few minutes after short-term (i.v. bolus) drug administration (a frequent occurrence during anaesthesia) there may be a substantial lack of pseudoequilibrium between drug concentrations in blood and drug effects in the vital organs such as the heart and brain. For example, there is often an "anticlockwise hysteresis" apparent on plots of the time-course of myocardial drug effects against the time-course of the systemic (arterial or peripheral venous) blood drug concentrations after short-term drug administration, which has often been attributed to a lack of pseudoequilibrium between the drug concentrations in blood and at the receptor sites responsible for drug action in the myocardium [1–3].

It has been suggested that arterial blood drug concentration should be better indicators of the duration and potency of drug effects because arterial blood carries drug to the sites of effect [4, 5]. Alternatively, the use of local venous blood drug concentrations has been proposed because these should be in pseudoequilibrium with tissue concentrations [4, 5]. It has also been proposed that drug concentrations at the receptor sites of a tissue should be in continuous equilibrium with drug concentrations in that tissue [6], and the magnitudes of drug effects on the myocardium therefore should be a function of the myocardial drug concentrations [7]. However, these relationships between drug concentrations in arterial or venous blood or the myocardium and drug effects on the heart after short-term i.v. drug administration are still uncertain.

This study compared the time-courses of the depression of myocardial contractility caused by i.v. bolus doses of lignocaine [8] with the simultaneously measured time-courses of its concentrations in arterial and coronary sinus blood, and in the myocardium determined using mass balance principles [9], in a chronically instrumented sheep preparation. The aim was therefore to determine which, if any, of these concentrations is related directly to the myocardial contractility depression induced by lignocaine. When this concentration has been identified, a knowledge of the determinants of its time-course may be used to explore avenues for optimizing the initial time-course of the myocardial effects of lignocaine.

MATERIALS AND METHODS

In this paper, aspects of the pharmacodynamic [8] and pharmacokinetic [9] data arising from a series of studies in five chronically instrumented adult female merino sheep are analysed and compared in detail.

Y. F. HUANG, M.B., B.S., PH.D.; R. N. UPTON, B.SC., PH.D.; W. B. RUNCIMAN, B.SC.(MED.), M.B., B.CH., F.F.A.R.A.C.S., PH.D.; Department of Anaesthesia and Intensive Care, Royal Adelaide Hospital, University of Adelaide, S.A. 5000, Australia. Accepted for Publication: December 9, 1992.

Correspondence to Y.F.H.

Relevant details of methods used in those studies [8, 9] are summarized here.

Sheep preparation

Sheep were prepared under anaesthesia (thiopentone for induction, 1.5% halothane for maintenance) with catheters in the ascending aorta, coronary sinus and inferior vena cava (IVC) via the carotid artery or jugular vein [8, 9]. An ultrasonic Doppler flow probe was placed on the left main coronary artery for measuring blood flow in this vessel [9]. A gas-powered system kept the intravascular catheters flushed with heparinized saline. Studies were conducted 1 week after the surgical preparations and at 2-day intervals thereafter while the sheep remained in their cages with free access to food and water.

Study design

Lignocaine hydrochloride in doses of 50, 75 or 100 mg was diluted to 10 ml with 0.9% saline immediately before each experiment. After a period of baseline haemodynamic measurements, a randomly selected dose was injected i.v. via the IVC catheter over 1 s [8, 9]. Pharmacodynamic and pharmacokinetic measurements were made for the next 15 min. The 50-, 75- and 100-mg doses of lignocaine were studied in five, four and five sheep, respectively.

Pharmacodynamic measurements. Left coronary artery blood flow velocity was measured continuously using an ultrasonic Doppler flowmeter and the Doppler flow probe placed on the left main coronary artery [9]. The maximum rate of increase in left ventricular pressure (LV dP/dt_{max}), used as an index of myocardial contractility, was obtained from the differentiated left ventricular pressure, which was measured continuously using a Millar Mikro-Tip pressure transducer catheter (Millar Instruments Inc., Houston, Texas, U.S.A.) placed in the left ventricle via one of the arterial catheters before each experiment [9].

Pharmacokinetic measurements. Paired blood samples were collected from the ascending aorta and the coronary sinus at up to 5-s intervals for 15 min after drug administration, using the sampling methods described previously [8, 10]. All samples were stored at −20 °C and the whole blood concentrations of lignocaine were assayed using a single extraction gas chromatographic method [11]. These concentrations and left coronary blood flow were used to calculate the time-courses of lignocaine concentrations in the myocardium perfused by the left coronary artery using mass balance principles. This method calculates the time-course of the myocardial drug concentrations from the net difference in flux of drug in the afferent (arterial) and efferent (coronary sinus) blood; its application to the myocardium has been described in detail previously [9, 12].

Data and statistical analysis

The following comparisons were made between the time-courses of the concentrations of lignocaine in arterial and coronary sinus blood and the myocardium, and the time-courses of the depression of myocardial contractility.

(1) The times of the peak arterial blood, coronary sinus blood or calculated myocardial lignocaine concentrations were compared with the times of the maximum depression of myocardial contractility. Note that the maximum depression of myocardial contractility described here refers to the observed maximum decrease in LV dP/dt_{max} under conditions of non-steady-state blood drug concentration (fig. 1).

(2) Lignocaine concentrations in the arterial blood, coronary sinus blood or the myocardium were plotted in time order against the percent decreases in myocardial contractility induced by lignocaine to examine for hysteresis and non-linearity in the concentration–effect relationships. If there was a time lag between concentration and effect (e.g. hysteresis), the plots were not superimposible and showed a clockwise or anticlockwise loop. To quantify the magnitude of hysteresis, each plot was divided into two sections at the point of the peak lignocaine concentration so that one section represented concentration–effect relationships when lignocaine concentrations were increasing, and the other represented the relationships when the lignocaine concentrations were decreasing. The area under each section of the curve (AUC) was calculated using the trapezoidal rule. Hysteresis was considered to be present when the differences between the AUC of these two sections of the hysteresis loop were statistically significant.

Two-sample *t* tests were used for the analysis of the AUC of the two sections of the hysteresis loops and the differences between the times of peak lignocaine concentrations and the times of maximum drug effect. Linear regression was used to correlate myocardial lignocaine concentrations and the percent decreases in myocardial contractility (LV dP/dt_{max}). $P < 0.05$ was considered statistically significant.

RESULTS

These subconvulsive doses of lignocaine induced significant and dose-dependent negative inotropic effects on the myocardium, as indicated by the decreases in LV dP/dt_{max}, in the absence of significant changes in heart rate or mean arterial pressure [8]. During the 15 min period after lignocaine administration, there was substantial lack of pseudoequilibrium between the myocardial lignocaine concentrations calculated using mass balance principles and lignocaine concentrations measured in arterial or coronary sinus blood [9]. The raw data for all the three dose groups are summarized in figure 1.

The times of the peak lignocaine concentrations in arterial blood, coronary sinus blood and myocardium are listed in table I. For all the doses, the times of the peak arterial blood lignocaine concentrations were approximately 26–38 s earlier than the times of maximum decreases in myocardial contractility. The times of the peak coronary sinus blood lignocaine concentrations were approximately 29–78 s later than the times of maximum decreases of myocardial contractility. With the exception of the 100-mg

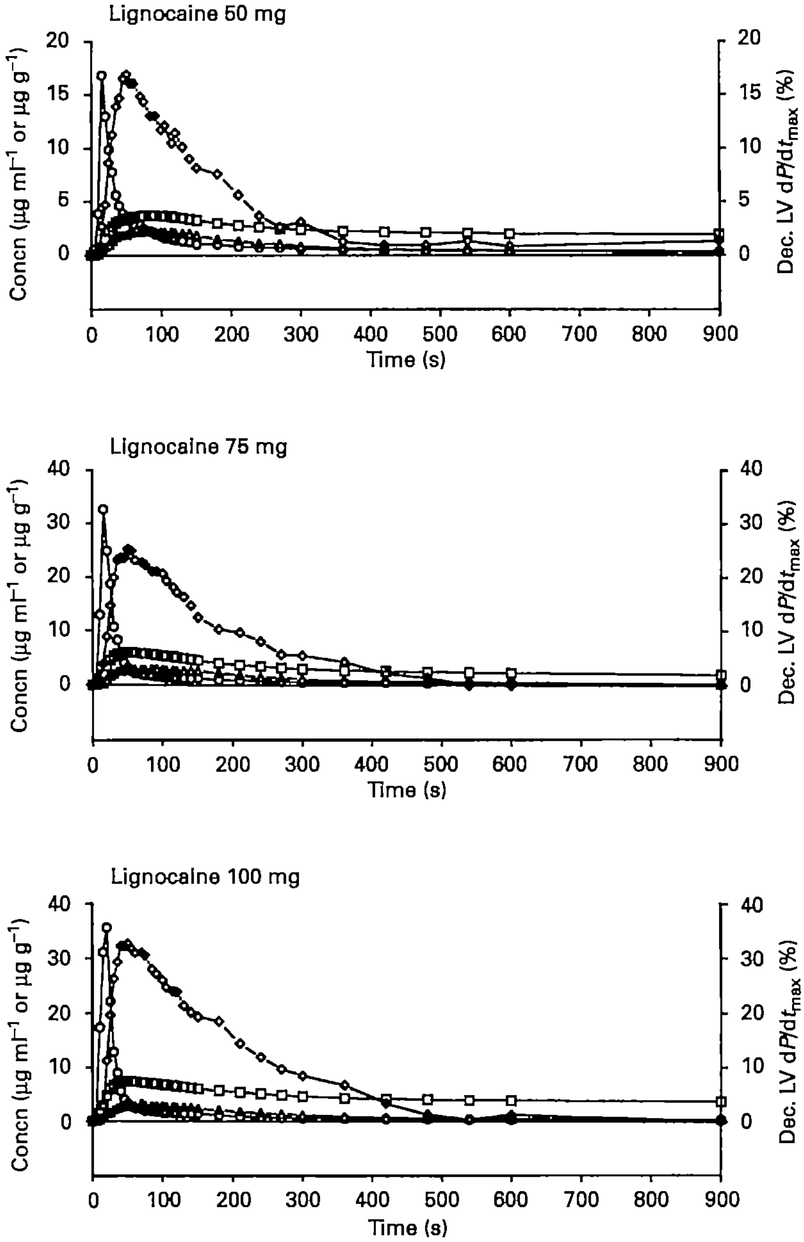


FIG. 1. Mean time-courses of lignocaine concentrations in arterial blood (○), coronary sinus blood (△) and the myocardium (□) (vertical axis at left) and the time-courses of the percent decreases (Dec.) in myocardial contractility (LV dP/dt_{max}) (◇) (vertical axis at right) from baseline after the 50- ($n = 5$), 75- ($n = 4$) and 100- ($n = 5$) mg doses of lignocaine.

doses of lignocaine, the times of the calculated peak myocardial lignocaine concentrations did not differ from the times of the maximum decreases in myocardial contractility (table I). For the 100-mg doses, the mean time of the peak lignocaine myocardial concentrations was 17 s later than the mean time of maximum myocardial contractility depression.

Examples of the percent decreases in LV dP/dt_{max} plotted against lignocaine concentrations in the arterial and coronary sinus blood and the myocardium after i.v. injection of 100-mg doses are shown in figure 2. The differences between the AUC under the sections when lignocaine concentrations were increasing and the sections when lignocaine concentrations were decreasing in the concentration–effect curves for the three doses are shown in table II. Significant anticlockwise hysteresis was present between the arterial lignocaine concentrations and the decreases of myocardial contractility in each dose group. No significant hysteresis was found between the coronary sinus blood lignocaine concentrations or the calculated myocardial lignocaine concentrations and the decreases of myocardial contractility.

A linear pharmacodynamic model [2, 13] was used to describe the myocardial lignocaine concentration–effect relationships. The data for the three doses were pooled together for this analysis. Linear regression between the myocardial lignocaine concentrations and the percent decreases of LV dP/dt_{max} were performed (fig. 3). The correlation coefficient (r) between myocardial lignocaine concentrations and the percent decreases in LV dP/dt_{max}

TABLE I. *Times of peak arterial blood, coronary sinus blood and myocardial concentrations of lignocaine and times of maximum depression of myocardial contractility (LV* dP/dt_{max}*) after the i.v. bolus injection of lignocaine in conscious, chronically instrumented sheep (mean (SD)). *Time significantly earlier or later than time of maximum depression* ($P < 0.05$)

	Time of peak drug concn (s)			Time of max. depression of LV dP/dt_{max} (s)
	Arterial	Coronary sinus	Myocardium	
Lignocaine dose				
50 mg ($n = 5$)	16 (2)*	83 (7)*	66 (23)	54 (11)
75 mg ($n = 4$)	15 (0)*	129 (43)*	55 (9)	51 (5)
100 mg ($n = 5$)	16 (4)*	85 (38)*	59 (14)*	42 (4)

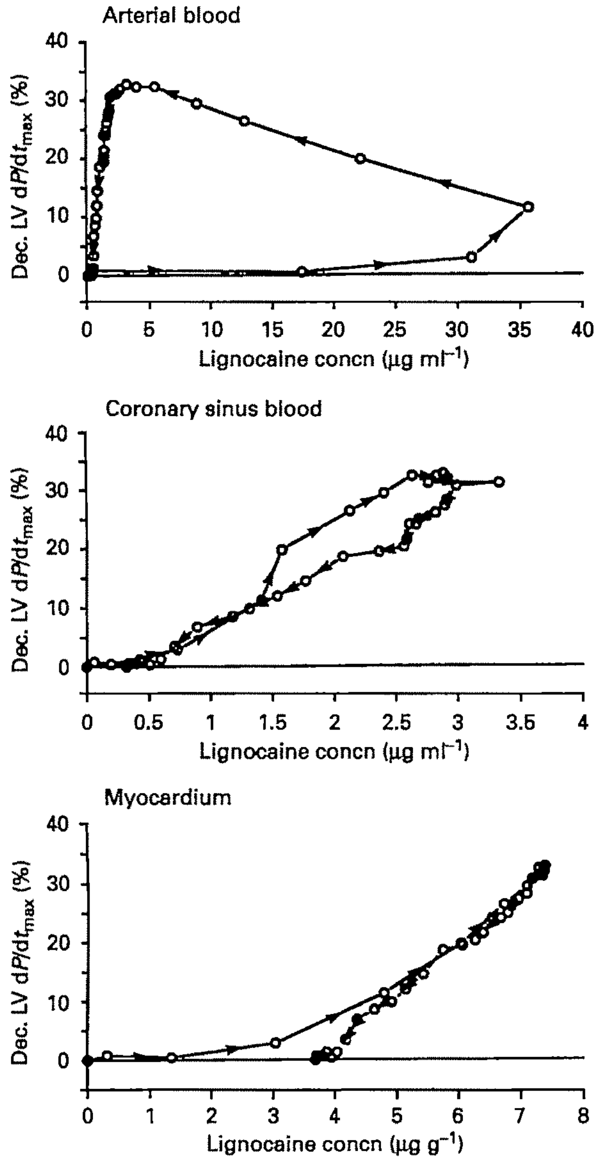


FIG. 2. Relationships between mean concentrations of lignocaine in arterial blood, coronary sinus blood and myocardium, and the mean percent decreases (Dec.) in myocardial contractility (LV dP/dt_{max}) after 100-mg doses ($n = 5$). Arrows show the time sequences of the concentration–effect relationships. Significant anticlockwise hystereses were found in arterial lignocaine concentration–effect relationships.

TABLE II. *Areas under the concentration–effect curves (AUC) were used to identify hysteresis in the arterial, coronary sinus blood and myocardial lignocaine concentration–effect relationships. The AUC under the section when lignocaine concentrations were increasing and the AUC under the section when lignocaine concentrations were decreasing were calculated for each experiment. The differences (mean (SD)) between these two sections are shown for the 50-* (n = 5)*, 75-* (n = 4) *and 100-* (n = 5) *mg doses. *Significant difference between AUC of the two sections* ($P < 0.05$)

	Dose of lignocaine (mg)		
	50	75	100
Arterial concentration–effect	1.59 (0.76)*	4.01 (2.91)*	8.74 (3.73)*
Coronary sinus concentration–effect	0.1 (0.14)	0.07 (0.62)	0.27 (0.23)
Myocardial concentration–effect	0.17 (0.26)	0.14 (0.14)	0.36 (0.24)

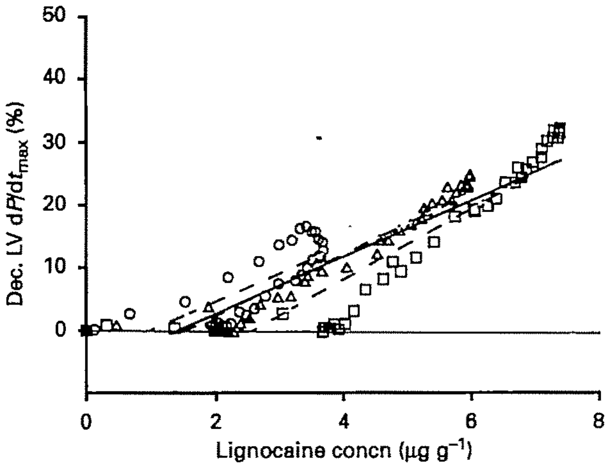


FIG. 3. Linear regressions between the mean myocardial concentrations of lignocaine and percent decrease in myocardial contractility (LV dP/dt_{max}). ○ = Lignocaine 50 mg; △ = lignocaine 75 mg; □ = lignocaine 100 mg. Dashed lines are the linear regressions for each dose group. Solid line is the linear regression for the pooled data of all the doses with an intercept of −4.45, slope of 4.44 and correlation coefficient 0.92.

was 0.92. The slope of this correlation was 4.4 and the intercept −4.5. Linear regression between myocardial lignocaine concentrations and the percent decreases in LV dP/dt_{max} also was performed for each dose group. The mean (SD) of the slopes of the 50-, 75- and 100-mg groups were 4.5 (2.7), 6.0 (2.4) and 5.7 (2.7), respectively. There was no significant difference among the individual slopes.

DISCUSSION

The technical difficulties of measuring myocardial drug concentrations in conscious animals without perturbing myocardial function have presumably contributed to the use of compartmental pharmacokinetic and pharmacodynamic models to describe and predict the relationship between myocardial drug kinetics and dynamics, because these models can be developed on the basis of blood drug concentration data [14]. Alternatively, the theoretical receptor site drug concentrations can be modelled using "effect compartment" pharmacokinetic and pharmacodynamic models such as those reported in the study of tubocurarine and thiopentone [15, 16]. In these models, the "receptor site" drug kinetics were linked to the central compartment by a first-order rate constant which was adjusted empirically so that hysteresis between drug concentrations at the receptor sites and drug effect disappeared. Although these models offer some resolution to the problem of hysteresis, their significance is limited by their lack of physiological reality [17]. In this study, lignocaine concentrations were measured or calculated at three sites relevant to myocardial drug kinetics and dynamics: arterial blood, coronary sinus blood and myocardium. Their usefulness in predicting drug effect is discussed in turn.

A poor relationship between the arterial blood concentrations of lignocaine and the decreases in myocardial contractility was shown by the differences between the times of the maximum decreases in myocardial contractility and the times of peak arterial blood concentrations of lignocaine (table I), and the *anticlockwise* hysteresis of the concentration–contractility relationships (fig. 2, table II), which suggests that these effects lag behind the arterial drug concentrations. Similar hysteresis between the arterial plasma concentrations of propofol, procainamide, lignocaine and their depressant effects on myocardial contractility after short term i.v. administration have also been reported [3, 18, 19]. The myocardial effects of some general anaesthetics were found to be poorly correlated with blood drug concentrations [20]. The lack of pseudoequilibrium between arterial blood and myocardial lignocaine concentrations reported in previous studies is the most likely explanation for these observations [9].

From the argument of Horowitz and Powell [21], it would be anticipated that the lignocaine concentrations in the myocardium would be better indices of the myocardial effects than its arterial concentrations. However, it should be remembered that methods based on mass balance principles determine the mean myocardial drug concentration, which may in itself be inadequate if the drug acts on specific sites of the myocardial cells that are not in pseudoequilibrium with the mean tissue concentration shortly after an i.v. bolus. Nevertheless, for all the doses used, good correlations were found between the myocardial lignocaine concentrations and the depression of myocardial contractility, with no significant hysteresis in the concentration–effect plots (table II, fig. 2). This provides evidence that lignocaine concentrations at the receptor sites responsible for the decrease of myocardial contractility were in pseudoequilibrium with the measured myocardial lignocaine concentrations [6].

A saturable concentration–effect curve was not observed in this study. However, during the first 20–30 s after lignocaine injection (represented by the first four points on the curve in figure 3), the myocardial lignocaine concentration–effect plots appear to curve upwards. After this period, the concentration–effect relationship was essentially linear. Because neither the concentrations nor the effects of lignocaine reached steady-state or their maximum values in this study, a linear pharmacodynamic model was used to describe the myocardial lignocaine concentration–effect relationship (fig. 3).

Myocardial drug concentrations are relatively difficult to monitor in patients [7]. As a simpler alternative, the effluent regional venous blood from the tissue or organ in which a drug exerts its effects could be used for the study of regional pharmacodynamics [4, 5]. This is an extension of the concept of venous equilibrium used in many physiological pharmacokinetic models in which the tissue and the effluent venous drug concentrations were related by a constant ratio—the partition coefficient. In this study, the coronary sinus blood concentrations of lignocaine were related relatively closely to the myocardial depressant effects (fig. 2, table II). However, the times of peak coronary sinus blood lignocaine concentrations were significantly later than the times of the maximum depression of myocardial contractility induced by lignocaine (table I). In this sense, the coronary sinus blood concentrations of lignocaine were not in equilibrium with the negative inotropic effects on the myocardium and therefore were not equivalent to the calculated myocardial concentrations of lignocaine, at least after such rapid i.v. drug administration. It would be expected that, in situations in which the blood drug concentration changes are slower than those which occur after i.v. bolus administration, the use of regional venous blood concentrations as indices of drug effect may have some merit, although a thorough knowledge of the relationships between regional venous and tissue drug concentrations would be an important prerequisite [22].

ACKNOWLEDGEMENTS

This study was supported by a grant from the National Heart Foundation of Australia. The authors thank Professor L. E. Mather for providing research facilities in the Department of Anaesthesia and Intensive Care of Flinders Medical Centre while those at the University of Adelaide were being refurbished. The authors also thank Dr J. P. Plummer for his statistical advice. Technical help from Mr K. Smart, Ms E. Henning and Ms C. Adcock is greatly appreciated.

REFERENCES

1. McAllister RG, Kirsten EB. The pharmacology of verapamil. IV. Kinetic and dynamic effects after single intravenous and oral doses. *Clinical Pharmacology and Therapeutics* 1982; **31**: 418–426.
2. Holford NG, Sheiner LB. Understanding the dose–effect relationship: Clinical application of pharmacokinetic–pharmacodynamic models. *Clinical Pharmacokinetics* 1981; **6**: 429–453.
3. Liem LB, Yee YG, Swerdlow CD, Kates RE. Pharmacodynamics of procainamide in patients with ventricular tachyarrhythmias. *Journal of Clinical Pharmacology* 1988; **28**: 984–989.
4. Chiou WL. The phenomenon and rationale of marked dependence of drug concentration on blood sampling site. Implications in pharmacokinetics, pharmacodynamics, toxi-

cology and therapeutics (Part I). *Clinical Pharmacokinetics* 1989; **17**: 175–199.

5. Chiou WL. The phenomenon and rationale of marked dependence of drug concentration on blood sampling site. Implications in pharmacokinetics, pharmacodynamics, toxicology and therapeutics (Part II). *Clinical Pharmacokinetics* 1989; **17**: 275–290.
6. Hull CJ. Pharmacokinetics and pharmacodynamics. *British Journal of Anaesthesia* 1979; **51**: 579–594.
7. Horowitz JD, Dynon MK, Woodward E, Benjamin ST, Macdonald SP, Morgan DJ, Goble AJ, Louis WJ. Short-term myocardial uptake of lidocaine and mexiletine in patients with ischemic heart disease. *Circulation* 1986; **73**: 987–996.
8. Huang YF, Upton RN, Runciman WB. I.v. bolus administration of subconvulsive doses of lignocaine to conscious sheep: myocardial pharmacokinetics. *British Journal of Anaesthesia* 1993; **70**: 326–332.
9. Huang YF, Upton RN, Rutten AJ, Runciman WB. I.v. bolus administration of subconvulsive doses of lignocaine to conscious sheep: Effects on circulatory function. *British Journal of Anaesthesia* 1992; **69**: 368–374.
10. Huang YF, Upton RN, Mather LE, Runciman WB. An assessment of methods for sampling blood to characterize rapidly changing blood drug concentrations. *Journal of Pharmaceutical Sciences* 1991; **80**: 847–851.
11. Nancarrow C, Runciman WB, Mather LE, Upton RN, Plummer JL. The influence of acidosis on the distribution of lidocaine and bupivacaine into the myocardium and brain of the sheep. *Anesthesia and Analgesia* 1987; **66**: 925–935.
12. Upton RN, Mather LE, Runciman WB, Nancarrow C, Carapetis RJ. The use of mass balance principles to describe regional drug distribution and elimination. *Journal of Pharmacokinetics and Biopharmaceutics* 1988; **16**: 13–29.
13. Schwinghammer TL, Kroboth PD. Basic concepts in pharmacodynamic modeling. *Journal of Clinical Pharmacology* 1988; **28**: 388–394.
14. Galeazzi RL, Benet LZ, Sheiner LB. Relationship between the pharmacokinetics and pharmacodynamics of procainamide. *Clinical Pharmacology and Therapeutics* 1976; **20**: 278–289.
15. Sheiner LB, Stanski DR, Vozeh S, Miller RD, Ham J. Simultaneous modeling of pharmacokinetics and pharmacodynamics: Application to d-tubocurarine. *Clinical Pharmacology and Therapeutics* 1979; **25**: 358–371.
16. Stanski DR, Hudson RJ, Homer TD, Saidman LJ, Meathe E. Pharmacodynamic modeling of thiopental anesthesia. *Journal of Pharmacokinetics and Biopharmacology* 1984; **12**: 223–240.
17. Hull CJ. How far can we go with compartmental models? *Anesthesiology* 1990; **72**: 399–402.
18. Binnion PF, Murtagh G, Pollock AM, Fletcher E. Relation between plasma lignocaine levels and induced haemodynamic changes. *British Medical Journal* 1969; **3**: 390–392.
19. Coetzee A, Fourie P, Coetzee J, Badenhorst E, Rebel A, Bolliger C, Uebel R, Wium C, Lombard C. Effect of various propofol plasma concentrations on regional myocardial contractility and left ventricular afterload. *Anesthesia and Analgesia* 1989; **69**: 473–483.
20. Christensen JH, Andersen F, Jansen JA. Pharmacokinetics and pharmacodynamics of thiopentone—A comparison between young and elderly patients. *Anaesthesia* 1982; **37**: 398–404.
21. Horowitz JD, Powell AC. Myocardial uptake of drugs and clinical effects. *Clinical Pharmacokinetics* 1986; **11**: 354–371.
22. Upton RN, Nancarrow C, McLean CF, Mather LE, Runciman WB. The *in vivo* blood, fat and muscle concentrations of lignocaine and bupivacaine in the hindquarters of sheep. *Xenobiotica* 1991; **21**: 13–22.

British Journal of Anaesthesia 1993; **70**: 562–573

REVIEW ARTICLE

THE MANAGEMENT OF ACUTE POISONING

G. G. COLLEE AND G. C. HANSON

Self poisoning is among the most common causes of non-traumatic coma in patients younger than 35 yr, and accounts for approximately 10% of all acute medical admissions [8]. Anaesthetists may become involved in the care of these patients during emergency resuscitation or in the intensive care unit. In the U.S.A., acute self poisoning accounts for 5–30% of admissions to medical intensive care units [21, 23].

Classification

Self-poisoning accounts for 95% of all poison-related admissions. It is slightly commoner in females (female to male ratio approximately = 1.3:1) with a peak incidence in females younger than 25 yr, and between 20 and 35 yr for males [8]. About 50% of all overdoses involve a mixture of agents [8, 10, 21]. Self-poisoning is often an impulsive act with no clear intent to die and with a previous history of similar episodes [33].

Accidental poisoning occurs predominantly in children younger than 5 yr, and may be with medicines (usually those prescribed to a parent) or household products. Each year accidental poisoning in children accounts for about 24000 hospital admissions in England and Wales [5]. Only about 15% of the children presented to hospital with accidental poisoning develop symptoms from the agent ingested [23]. Fatal accidental poisoning is rare [35].

Non-accidental poisoning may occur as an extension of the syndrome of child abuse, usually in children younger than 30 months. This may be more common than is generally accepted [7], and has a fatal outcome more commonly than cases of accidental poisoning [23].

Homicidal poisoning is encountered rarely in clinical practice.

Diagnosis

Diagnosis is usually made from the history and circumstantial evidence. However, patients' statements about the nature and the quantity of the poison ingested are unreliable [39]. Witnesses, family, friends and ambulance personnel should be interviewed to establish details regarding the probable agents ingested and approximate time of ingestion. Alcohol is often taken in combination with one or more other agents.

Isolated signs and symptoms are of little diagnostic value in any poisoning incident, but identification of the agent can often be surmised from the history and examination. Various combinations of signs may be suggestive of specific commonly ingested poisons [11]; however, there is a poor correlation between drugs suspected on admission and those actually detected in the blood [21]. The agents used in deliberate self-poisoning undergo changing patterns, with various agents going in and out of vogue. Currently in the U.K., the agents encountered most commonly in deliberate self-poisoning are the benzodiazepines, paracetamol, aspirin and tricyclic antidepressants [8]. Car exhaust poisoning is the method of suicide used most often by men aged 15–44 yr [29].

Toxicological screening should be considered in the urgent investigation of coma when the history, examination and biochemical analysis do not yield a diagnosis. About 50% of patients attending a casualty department with coma of unknown aetiology may be self-poisoning cases [10]. Appropriate samples should be collected early in the initial management of these patients so that they are available later if required for either diagnostic or medico–legal purposes. These samples should include:

Gastric contents: 50 ml of vomit, aspirate or the first portion of a gastric lavage.

Urine: 50 ml of the first sample voided after admission.

Blood: 10 ml of lithium–heparinized blood, 10 ml of blood without anticoagulant, and 2 ml of fluorided blood for ethanol assay. Care should be taken to avoid the use of swabs containing alcohol.

Ideally, all of these samples should be collected before administration of any medications which may confuse toxicological analysis.

Routine biochemical and haematological investigations may, rarely, suggest a diagnosis of acute poisoning. More often they provide a helpful baseline for later comparison. Many poisons cause fluid and electrolyte imbalance, renal or hepatic impairment, or acid–base imbalance.

The majority of patients admitted after acute

(Br. J. Anaesth. 1993; **70**: 562–573)

KEY WORDS
Toxicity: drugs.

George G. Collee, M.B., Ch.B., F.R.C.Anaes., Department of Anaesthesia, St Bartholomew's Hospital, London EC1A 7BE. Gillian C. Hanson, M.B., F.R.C.P., F.R.C.Anaes., Whipps Cross Hospital, Whipps Cross Road, Leytonstone, London E11 1NR.
Correspondence to G.C.H.

poisoning are conscious on arrival at the hospital; however, in unconscious patients organic brain damage should always be suspected if the history of poisoning is unsatisfactory and the depth of coma does not improve within 12 h.

MANAGEMENT

Before consideration of the active management of the poisoned patient, it should be emphasized that, for the majority of poisoned patients, only supportive care is needed. This led one reviewer to comment "It cannot be repeated too often that the primary object of the treatment of acute poisoning is not to collect as much 'poison' from the patient as possible, but to save life when this is threatened and to relieve pain and suffering... i.e.... to save the patient, not to regain the poison" [22].

Immediate measures

Initial resuscitation in comatose patients should be conducted with the usual priorities: A–B–C–D–E:

Airway. Provide one if the patient's upper airway is obstructed. Protect the airway if the cough and gag reflexes are obtunded and secure the airway, when necessary, with tracheal intubation (this may include patients with marginally adequate protective reflexes who require gastric lavage).

Breathing. Assess the ventilatory efforts and assist where necessary. Assess gas exchange. Look for evidence of aspiration of gastric contents, toxic gases or foreign substances.

Circulation. Establish i.v. access early. Assess peripheral perfusion and begin resuscitation as required. Connect electrocardiographic monitoring and examine a rhythm strip.

Collect samples for future toxicological analysis if required.

Document the available history before ambulance personnel, relatives, etc. leave the hospital, and the level of coma.

Examine the patient thoroughly for associated injuries (e.g. pressure area necrosis), medical conditions which may have precipitated the overdose (e.g. toxic psychosis) or which may produce coma (e.g. hypoglycaemia).

Measures to limit absorption

The conventional belief that, after ingestion of poisons other than corrosives or petroleum distillates, the stomach should be routinely emptied by emesis or gastric lavage has been questioned by several authors [25, 27, 37].

Emesis should be induced only in fully conscious patients. It is less traumatic for the conscious patient than gastric lavage and is therefore the preferred technique of gastric emptying for children. However, the recovery of gastric contents by ipecacuanha-induced emesis is generally less than 50% [28, 37]. Syrup of ipecacuanha followed by an adequate volume of water induces vomiting in 90–95% of patients within 20–30 min, in both adults and children [13, 32]. Evidence that this emesis significantly reduces the absorption of commonly ingested poisons is less convincing. Therefore, although it only rarely causes serious sequelae, it is probably of little or no benefit to the majority of poisoned patients. The decision to empty the conscious patient's stomach by inducing emesis should be dependent upon the specific history of probable toxins, the estimated dose and the time since ingestion, rather than an automatic response to a history of acute poisoning.

Gastric aspiration and lavage is the only suitable way of emptying the stomach in the presence of obtunded laryngeal and pharyngeal reflexes. Airway protection is an essential part of the procedure. In the semi-conscious patient, airway protection may be achieved by placing the patient in the left-lateral, head-down position in the presence of an experienced anaesthetist with suction apparatus immediately to hand. In patients with more severely obtunded reflexes, it is safer to opt for elective tracheal intubation before gastric lavage.

Gastric aspiration and lavage via a wide-bore orogastric tube is indicated within 4 h of serious poisoning (i.e. the patient is comatose) with any of the commonly ingested poisons. The technique has been well described elsewhere [26]. Because the history is usually unreliable and gastric emptying is delayed by many poisons (notably aspirin and the tricyclic antidepressants), gastric lavage should be considered in any seriously poisoned patient up to 12 h after ingestion [12]. Conversely, with drugs which do not delay gastric emptying and which are absorbed rapidly from the gastrointestinal tract (e.g. paracetamol), gastric lavage may be ineffective as little as 2–4 h after ingestion.

Activated charcoal is a powerful, non-specific adsorbent which may be administered orally or via a gastric tube. Irreversibly binding the drugs within the bowel reduces blood concentration both by reducing drug absorption and by creating a negative diffusion gradient between the gut lumen and the blood, whereby drug diffuses from the circulation into the gut lumen—so called "gastrointestinal dialysis" [18]. It may be appropriate, therefore, to administer activated charcoal long after the original poisoning, and repeated administration is advocated as a safe, cheap and effective method of reducing drug concentrations in the blood. It is of demonstrable benefit after poisoning with several commonly ingested drugs, including aspirin [20] and paracetamol [19]. Anecdotal reports support the use of repeated administration of activated charcoal after a variety of other poisons. Enthusiasm for these relatively unproven uses, however, must be tempered by reports of serious consequences of pulmonary aspiration of activated charcoal [9, 24] and the minor risk of gastrointestinal obstruction after its use [36]. Furthermore, there are theoretical limitations. Drug elimination with activated charcoal is less effective in patients with severely impaired gastrointestinal motility—particularly relevant after poisoning with salicylates or with agents which have a significant anticholinergic action. Kirshenbaum and colleagues have questioned the clinical efficacy of multiple-dose charcoal therapy after salicylate poisoning [16]. It is suggested also that clearance of parenterally administered medications used to treat intoxicated patients is increased by the charcoal, perhaps making treatment less effective.

Further pharmacokinetic data on the clearance of specific poisons are needed to determine the rational use of repeated charcoal regimens in a variety of clinical settings. Meanwhile, it provides a relatively safe technique of proven benefit in limiting drug absorption when given soon after ingestion of specific poisons. It is also probably of benefit in repeated doses in carefully selected clinical circumstances. Drugs which are well adsorbed to activated charcoal include benzodiazepines, antidepressants, anticonvulsants, barbiturates and theophylline. Salicylates and paracetamol are moderately well adsorbed.

Supportive care

All but a small minority of unconscious poisoned patients recover with supportive care alone. Conservative therapy is aimed at preventing complications such as hypoxaemia, aspiration, hypotension, acid–base and electrolyte imbalance, hypothermia, convulsions and the consequences of unconsciousness, whilst awaiting spontaneous elimination of the poison via the liver, kidneys, lungs and gut.

Respiratory complications are the commonest causes of death after acute poisoning, and immediate management must give priority to the airway, ventilation and prevention of aspiration. Having established an airway, it is important to assess the protective reflexes and consider the need for tracheal intubation. Whether or not gastric lavage is considered appropriate, a nasogastric tube should be inserted to prevent gastric dilatation. Hypoventilation is common after poisoning with sedatives, hypnotics, analgesics and many other drugs and chemicals. Hypoxia and hypercapnia may cause or potentiate cardiac arrhythmias or may exacerbate increased intracranial pressure, and should therefore be treated promptly. Specific antidotes may play a role in reducing the need for mechanical ventilation after poisoning with opioids or benzodiazepines (see *Neurological complications*).

Continued observation is essential in order to detect deterioration in the conscious level requiring a reappraisal of the need for airway protection or mechanical ventilation. Nurses should be given *specific* criteria by which to assess the need for re-referral to an anaesthetist. All patients requiring mechanical ventilation or tracheal intubation should be transferred to an intensive care unit for further monitoring.

Patients may present after long periods of respiratory depression, having already developed aspiration pneumonia or hypostatic pneumonia. The mainstay of treatment comprises endobronchial aspiration, physiotherapy and antibiotics.

Cardiovascular complications include hypotension, cardiac arrhythmias and cardiac arrest. A careful assessment of the patient's cardiovascular status should be made soon after presentation. The major factors contributing to hypotension in the presence of normal sinus rhythm are peripheral vasodilatation and myocardial depression, and the majority of patients respond to adequate intravascular volume repletion. In young, previously healthy patients, invasive monitoring is rarely required.

Arrhythmias may be caused by the toxin (e.g. poisoning with tricyclic antidepressants), hypoxia or hypercapnia, or may be secondary to the effects of the toxin on acid–base or electrolyte balance. A 12-lead ECG should be performed to provide a baseline and, in selected patients, continuous ECG monitoring is required. Patients suffering cardiac arrest as a direct result of a circulating toxin may be resistant to attempts to re-establish sinus rhythm. It is therefore worth persisting with external cardiac massage for longer than may otherwise be considered appropriate. Particular caution should be exercised in attributing any significance to the presence of fixed dilated pupils, which may reflect merely the actions of the toxin rather than any cerebral dysfunction.

Renal complications may result from the direct effects of the toxin (e.g. in aspirin, paracetamol or heavy metal poisoning), from a period of hypotension, from rhabdomyolysis with myoglobinuria, or from sepsis related to aspiration pneumonia. For further information beyond the scope of this article, the reader is referred to an extensive review of nephrotoxins by Abuelo [1].

Myoglobinuria should be suspected in any patient with evidence of a prolonged period of coma before admission (i.e. pressure area discolouration with poor capillary refill), with a history of prolonged seizures or with tissue hypoxia (e.g. from carbon monoxide poisoning).

Any comatose or hypotensive patient, or any patient with a history of poisoning with a known nephrotoxin, should be catheterized, and the urine output maintained at least at 0.5 ml kg^{-1} h^{-1}. This is achieved with volume resuscitation in the first instance followed, if necessary, by an infusion of dopamine in a small dose (2–4 μg kg^{-1} min^{-1}) and the judicious use of diuretics. Urinalysis before intervention may aid diagnosis by pointing to a renal or pre-renal cause, and occasionally by displaying the granular casts of acute tubular necrosis or the eosinophils of an acute interstitial nephritis.

When rhabdomyolysis is suspected, urinalysis of myoglobin should be performed, but treatment should be started promptly without awaiting the results of urinalysis. Urine output should be maintained at least at 1.5–2 ml kg^{-1} h^{-1} with aggressive volume loading and mannitol, and the urinary pH should be kept greater than 6.5 in order to prevent myoglobin from precipitating in the renal tubules. Loop diuretics have the theoretical disadvantage of acidifying the urine, therefore mannitol is preferred for maintaining the diuresis. Blood samples should be taken for measurement of the urea, creatinine, potassium, calcium and creatine phosphokinase concentrations. In severe cases, hypocalcaemia may result from a shift of extracellular calcium into injured muscle. Serum potassium concentrations may increase rapidly because of muscle breakdown, necessitating early intervention with calcium, glucose and insulin infusion, or dialysis.

Hepatic and gastrointestinal complications. Gastric stasis may occur in any comatose patient, or in response to anticholinergic or opioid effects. Early decompression with a nasogastric tube should be performed to reduce the risk of regurgitation and aspiration. Stress ulcer prophylaxis may also be appropriate in selected patients.

Fulminant hepatic failure is a well recognized complication of serious poisoning with paracetamol, carbon tetrachloride or *Amanita phalloides.* These patients require early referral to a specialist liver unit.

Neurological complications include depression of conscious level, seizures, cerebral oedema and peripheral nerve injuries as a result of prolonged pressure. It is important to exclude metabolic or traumatic causes, and any patient whose level of consciousness appears inappropriately depressed for the history of poisoning should be suspected of having an intracranial haemorrhage. Lateralizing signs are rarely attributable directly to the toxin.

Correct nursing care is essential to protect the patient from the complications of prolonged coma. The presence of pressure area necrosis, neuropraxias, corneal abrasions and other sequelae of coma must be documented on admission to the unit, both to alert the nurses to areas requiring special attention, and to provide medico–legal protection. The role of specific antagonists such as naloxone and flumazenil to antagonize central nervous system depression is controversial [2]. Reversal of coma can undoubtedly make management of the patient easier; however, acute antagonism of opioids with naloxone, or of benzodiazepines with flumazenil, may provoke severe withdrawal reactions. Antagonism of benzodiazepines with the specific antagonist, flumazenil, may be counterproductive in patients who have taken a mixture of drugs. For example, in the commonly encountered poisoning with both tricyclic antidepressants and benzodiazepines, acute antagonism of the benzodiazepines may induce seizures which had previously been suppressed. Moreover, for both antagonists the action of the antagonism is short-lived, therefore the patient may become comatose unexpectedly as the antagonist wears off.

Seizures may result from metabolic disturbance, cerebral hypoxia, or as a direct toxic effect (e.g. after poisoning with tricyclic antidepressants or theophylline). Urgent control is essential and is usually achieved initially with i.v. diazepam. Thereafter, consideration must be given to further anticonvulsant therapy (e.g. with phenytoin, phenobarbitone or clonazepam). Resistant subjects may require an infusion of thiopentone. Some of these agents cause further respiratory depression and elective tracheal intubation and artificial ventilation may be necessary. Detection of further seizures may be difficult in the patient undergoing ventilation, and monitoring should include continuous recording with a cerebral function monitor if neuromuscular blockers are used.

Cerebral oedema should be anticipated in any patient who has suffered a hypoxic cardiac arrest, a period of profound hypotension or severe carbon monoxide poisoning. Treatment to prevent secondary brain injury should include elective intubation and mechanical ventilation to moderate hypocapnia, with careful control of cerebral perfusion pressure by maintaining the mean arterial pressure within the normal range for that patient, and by avoiding fluid overload. Mannitol and loop diuretics may have a role after specialist consultation, and in severe cases intracranial pressure monitoring may be appropriate to direct therapy.

Metabolic complications may take almost any form in acute poisoning. The concentrations of urea, electrolytes and blood glucose should be checked routinely. In some patients, blood-gas analysis is also required.

Hypothermia is a common complication of prolonged coma outside hospital, and may be exacerbated by drugs which prevent the usual responses of vasoconstriction and shivering. Passive rewarming should be achieved with warm blankets. Active external rewarming is discouraged, as it may produce peripheral vasodilatation when cardiac function is still depressed by a reduced core temperature. I.v. fluids should be warmed and, during artificial ventilation, warm water bath humidifiers should be added to the breathing system. In extreme cases (< 32 °C) resistant to these techniques, it may be necessary to rewarm actively with warm water gastric or bladder instillation or by peritoneal lavage. Temperature should be monitored centrally (oesophageal or nasopharyngeal) and the ECG should be monitored for arrhythmias.

Hyperthermia may occur in acute intoxication with, for example, tricyclic antidepressants, cocaine or amphetamines, or as part of the syndrome of neuroleptic malignant syndrome after phenothiazine overdosage. In severe cases, active cooling with sedation, paralysis and ventilation with unheated gases may be required to control core temperature.

Measures to enhance elimination of the poison

Fewer than 5% of cases of acute poisoning merit treatment with specific techniques to increase drug elimination [34]. "*Gastrointestinal dialysis*" with activated charcoal has already been discussed, and for those drugs which are readily adsorbed to activated charcoal it provides the safest mechanism of enhancing drug clearance. More invasive techniques are rarely justified. In cases of serious poisoning, specialist advice should be sought from the regional poisons centre.

Forced diuresis should be considered only for those patients in whom toxicological analysis has demonstrated the presence in the blood of a toxic agent in sufficient amount to cause severe poisoning. Brisk diuresis maintains a small concentration gradient between the renal tubular fluid and the renal capillary bed, thereby minimizing tubular reabsorption of toxins. Manipulation of the urinary pH may further decrease tubular reabsorption of the targeted drug by ensuring that it remains mostly in the ionized form. Therefore, for weak acids (such as salicylates or barbiturates), forced alkaline diuresis is most effective, whilst for weak bases (such as phencyclidine) forced acid diuresis is more appropriate. The technique is ineffective for drugs which are strongly protein-bound (e.g. tricyclic antidepressants, carbamazepine, phenytoin) or which have a large apparent volume of distribution (e.g. paracetamol, lithium, tricylic antidepressants). Regimens to establish a forced alkaline or forced acid diuresis have been described well elsewhere [34]. The technique, however, carries significant risk of causing fluid overload with pulmonary oedema or cerebral oedema, or of causing severe disturbance of electrolyte and acid–base balance. This risk is accentuated in the elderly, or those with cardiac or renal impairment, and should be balanced against the likelihood of significantly altering the patient's clinical outcome.

Extracorporeal elimination techniques—haemodialysis and haemoperfusion—have not yet been assessed adequately clinically in acute poisoning, and there remain many difficulties in assessing the efficacy of these invasive techniques [4, 38]. Their use should currently be limited to a carefully selected group of patients, and specialist help should always be sought. For extracorporeal elimination techniques to be helpful the following criteria are suggested [4]:
(1) The drug or toxin should either diffuse readily through the dialysis membrane or be readily taken up by an absorbant. Protein-bound drugs and large molecules are removed inefficiently by dialysis, and can be removed more effectively by haemoperfusion (in which the blood is passed directly over sorbent particles to which toxins or drugs are adsorbed by surface forces). However, although salicylates are protein-bound, the plasma binding sites are saturated quickly even at normal therapeutic plasma concentrations, therefore a large proportion of the drug exists in the unbound form.
(2) A significant proportion of the poison should be present in the plasma water, or be capable of rapid equilibration with it. Drugs with a large volume of distribution and high lipid solubility are therefore difficult to eliminate. If movement of the drug from the extravascular compartment back into the intravascular compartment is slower than the plasma clearance achieved, a rebound of the plasma concentration occurs on stopping dialysis/haemoperfusion.
(3) The pharmacological effect of the toxin should be directly related to its concentration in the blood.
(4) Dialysis or haemoperfusion should add significantly to other body mechanisms of elimination.

Peritoneal dialysis achieves considerably less clearance of plasma than can be achieved with haemodialysis, and has no established role in the management of acute poisoning.

Haemodialysis or haemoperfusion has a clearly established role in the treatment of severe salicylate overdosage or poisoning with death cap mushrooms (*Amanita phalloides*) [4]. Clearance of alcohol, ethanol, barbiturates, anticonvulsants, benzodiazepines, lithium, cardiac glycosides and many other less commonly encountered poisons can certainly be enhanced with extracorporeal techniques; however, it remains unclear if this influences clinical outcome favourably. Clearance of paracetamol and the tricyclic antidepressants is not enhanced by haemodialysis or haemoperfusion, and extracorporeal elimination techniques have no role in the management of patients after poisoning with these agents.

Use of specific antidotes

The toxic effects after poisoning with specific agents may be decreased or prevented by administration of their specific antidotes. Such antidotes may directly influence the metabolism of the poison, preventing or reducing the formation of harmful metabolites (e.g. acetylcysteine in paracetamol poisoning), may compete for drug receptor sites (e.g. flumazenil in benzodiazepine overdose; naloxone in opioid overdose) or may bind with the poison to form less toxic chelates which are more easily excreted (e.g. Fab fragments in severe cardiac glycoside overdosage). A broader definition of an antidote includes any substance which can favourably influence the onset, severity or duration of the toxic effects of a poison. The currently available antidote therapies and their clinical use has recently been reviewed comprehensively by Lheureux, Even-Adin and Askenasi [17] and emergency departments should keep a reference list of antidotes and their mode of administration for quick reference.

FEATURES AND TREATMENT OF SPECIFIC POISONS

It is proposed not to give here detailed aspects of management, but to provide a ready, practical referral list, and to point out aspects of care peculiar to specific intoxicants.

Analgesics

Salicylate intoxication

A large number of salicylate preparations are available to the community, many of which do not mention the name "aspirin". Oil of wintergreen is methyl salicylate and is highly toxic.

Pharmacology. In normal therapeutic doses, acetyl salicylic acid is de-acetylated by plasma esterases and eliminated by conjugation. The volume of distribution is normally low but, when metabolic acidosis develops, tissue penetration increases.

In salicylate intoxication, prolongation of elimination occurs, the conjugation pathway rapidly becomes saturated and elimination is by the clearance of free salicylate via the kidneys. Salicylate clearance is pH-dependent, increasing 10-fold from a serum pH of 6 to that of 7.5.

Salicylates have a contradictory effect on acid–base balance. CNS stimulation of the respiratory centre may lead to respiratory alkalosis, whereas salicylate itself results in the accumulation of organic acid metabolites. The interaction between these two elements is variable and can be assessed only by frequent measurement of blood-gas tensions and acid–base state. Other important metabolic effects are hypo- or hyperglycaemia, and hypokalaemia from compensatory renal excretion.

There is increased risk of permeability-related oedema, although left ventricular failure may also occur secondary to cardiac arrhythmias, hypokalaemia or fluid overload. Clotting defects may

TABLE I. *Summary of management of salicylate poisoning*

Mild intoxication
  Observe fluid balance.
  Forced diuresis with large fluid turnover (4 litre/24 h).
  Repeat salicylate concentration measurement 2 h later to check that concentration is decreasing.
Moderate–severe intoxication
  Admit to ITU regardless of the level of consciousness.
  Administer activated charcoal orally or via a nasogastric tube: 5 g 4-hourly for six doses.
  Observe airway, ventilatory frequency, mental state and core temperature.
  Insert central venous pressure cannula.
  Measure acid–base balance 2-hourly.
  Forced alkaline diuresis.
  Maintain careful fluid balance charts and observe for fluid overload, pulmonary oedema and pulmonary aspiration.
  Haemodialyse if:
  1. "Severe" concentration does not decrease after 2 h of therapy.
  2. "Moderate" concentration increases to the "severe" range after 2 h of therapy.
  3. Onset of acute renal failure or pulmonary oedema secondary to fluid overload, unresponsive to diuretic therapy.

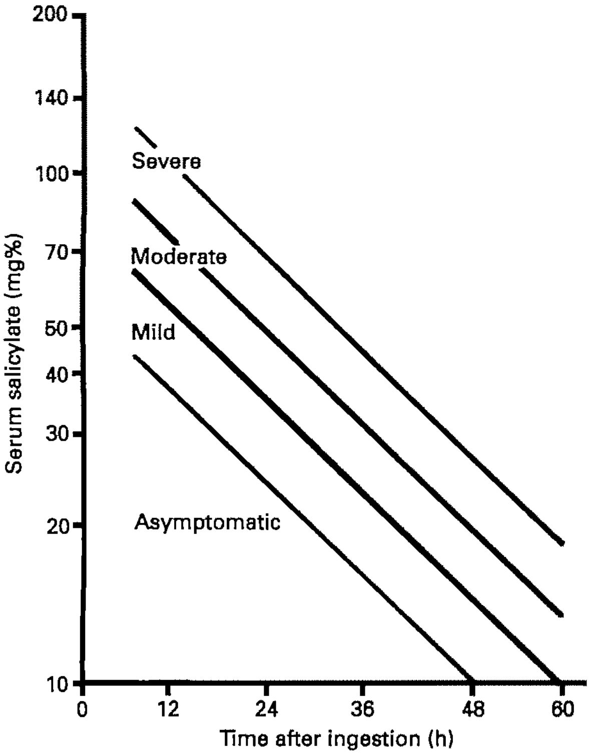


FIG. 1. Nomogram relating the serum salicylate concentration and expected severity of intoxication at varying intervals after ingestion of a single dose of salicylate (salicylate 13.8 mg = 1 mmol). (After Done, 1960 [6]; reproduced by permission of *Pediatrics*.)

occur because of inhibition of Factor VII production by salicylate.

Presentation. Restlessness, irritability and hallucinations; tinnitus; tachycardia; hyperventilation; pyrexia, sweating; occasionally, pulmonary oedema.

General management (table I). Gastric lavage if ingestion < 24 h. Activated charcoal in repeated doses via a nasagastric tube. Check salicylate concentration, blood-gas tensions, and concentrations of electrolyltes, clotting factors and blood glucose.

In severe intoxication (fig. 1), check also serum concentrations of proteins and calcium, and liver function tests. Hyperpyrexia is rare, but may require treatment.

Fluids and electrolytes. Ensure intravascular volume repletion with colloid, then give 1 litre of saline 1 mol litre^{-1} or 0.3 mol litre^{-1} every 4–6 h. Monitor urinary pH. If < 7.2, give 1 litre of saline 0.3 mol litre^{-1} with sodium bicarbonate 100 mmol i.v. over the subsequent 2 h, and review urinary pH. *Do not give more than 300 mmol of sodium per 24 h.*

Repeat measurement of the blood salicylate concentration after 2 h. If a "moderate" concentration has increased to the "severe" range, or there has been no decrease from the severe range, commence renal dialysis, or refer for renal dialysis. If there has been a decrease in the salicylate concentration, try to maintain the urinary pH > 7.2 with the use of sodium bicarbonate 50–100 mmol added to 1 litre of saline 0.3 mol litre^{-1}. Potassium chloride 60–120 mmol should be added to each 1 litre of i.v. solution.

Observe serum sodium, potassium and bicarbonate concentrations and pH.

Avoid fluid overload, metabolic alkalosis, hypernatraemia and hypokalaemia.

Should there be doubt about the fluid balance or the patient develops pulmonary oedema, pulmonary artery occlusion pressure monitoring is essential. A small pulmonary artery occlusion pressure should be aimed for.

Paracetamol intoxication

Pharmacology. Paracetamol is converted initially in hepatocytes to the potentially toxic metabolite n-acetyl-p-benzoquinoneimine (NABQI), which is conjugated rapidly to glutathione within the cell. In paracetamol overdose, glutathione stores are overwhelmed and unconjugated NABQI binds to proteins within the cell, producing necrosis. Increased concentration of intracellular calcium appears to play a fundamental role in the induction of cellular injury.

Paracetamol-induced liver damage is likely to be worse in patients taking hepatic enzyme-inducing agents, such as barbiturates or alcohol.

Paracetamol intoxication may also be complicated by renal failure and myocardial necrosis.

Presentation. Early (< 24 h): nausea and vomiting; confusion (occasionally); signs may be masked by additional drug ingestion. Late (> 24 h): severe vomiting; jaundice; evidence of acute hepatic failure, including encephalopathy, bruising and hypoglycaemia.

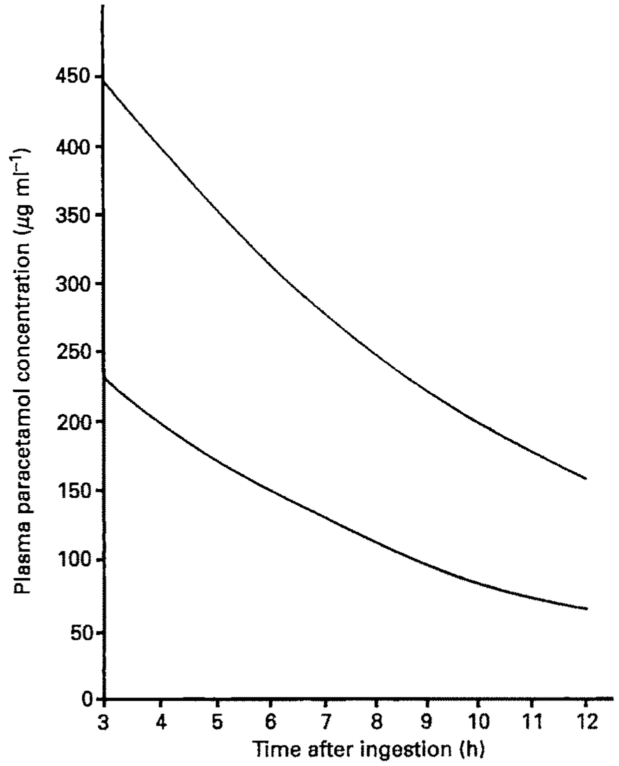


FIG. 2. Plasma paracetamol concentrations in relationship to time after overdose. Liver damage is likely to be severe above the upper line, mild to severe between the lines, and clinically insignificant under the line. (From Prescott and colleagues 1976 [30]; reproduced by permission of L. F. Prescott.)

Any patient with suspected intoxication MUST have a toxicological screen for paracetamol.

Management: gastric lavage within 4 h of ingestion, and antidote therapy.

There is now evidence to support the treatment of all patients with paracetamol intoxication with an antidote, regardless of the time of presentation, even if treatment is initiated when the patient has established fulminant hepatic failure [14].

The antidote should be used in patients who present at less than 8 h if more than 7 g of paracetamol has been ingested, or if the plasma concentration of paracetamol is above the lower line on the plot of paracetamol concentrations in relationship to time after overdose, shown in figure 2. Patients receiving enzyme-inducing agents should be treated at 70 % smaller concentrations.

At early presentation (within 8 h of ingestion), methionine may be given (2.5 g immediately, followed by three further doses 4-hourly). Patients presenting more than 8 h after ingestion of paracetamol should have their plasma paracetamol concentration assayed immediately. Antidote should then be given without delay and the paracetamol concentration checked again 4 h later. Failure of the plasma paracetamol concentration to decrease by 50 % may signify impending liver damage.

The antidote regimen should comprise acetylcysteine i.v. 150 mg/kg body weight in 5 % glucose 200 ml over 15 min, followed by 50 mg/kg body weight in 5 % glucose 500 ml over 4 h, followed by 100 mg/kg body weight in 5 % glucose 1000 ml over 16 h.

Occasionally, a histamine-mediated reaction develops in response to acetylcysteine.

Other aspects of management. Check clotting factors, electrolyte concentrations and liver function tests. Monitor capillary blood glucose concentration hourly. Monitor the patient's level of consciousness. Give glucose by i.v. infusion, to a total of 300 g daily. Observe for onset of renal failure. Renal dialysis may be necessary.

If ingestion was more than 24 h before presentation, and intoxication is assumed to be moderate to severe, observe for evidence of hepatocellular failure (deteriorating level of consciousness; increasing prothrombin time; pH less than 7.3) and introduce routine therapy for liver failure (these patients should be treated in an intensive therapy unit).

Referral to a centre particularly interested in the management of patients with paracetamol intoxication should be considered under the following circumstances [15]:

pH < 7.3 more than 24 h after ingestion
Prothrombin time > 45 s at 48 h
> 50 s at 72 h
Increasing serum creatinine concentration
Rapid development of grade 2 encephalopathy

Liver transplantation may be considered under the following circumstances [15]:

pH < 7.3
Prothrombin time > 100 s
Serum creatinine concentration > 300 μmol litre^{-1}
Coma grade 3 or 4
Increasing prothrombin time from day 3 to day 4 after overdose.

Cocaine intoxication

Pharmacology. Cocaine (benzoylmethylecognine) is absorbed from all mucosal surfaces and is most commonly taken i.v., by insufflation (intranasal) and by smoking (pulmonary). When it is insufflated, the peak action occurs at 30 min and lasts 60 min. The pharmacokinetic properties of i.v. cocaine are similar to those of smoked or inhaled cocaine.

"Crack" is the poorly water-soluble alkaloid form of cocaine, and is smoked. The onset of action is within minutes, and is dissipated within 20 min.

If ingested with alcohol, cocaine may be metabolized in the liver to a longer lasting more lethal metabolite [31].

Presentation. Clinical effects are the result of both peripheral and central nervous system stimulation. CNS stimulation: Euphoria, agitation, confusion; seizures; hyperthermia.

Peripheral vasomotor stimulation by noradrenaline results in tachycardia and hypertension.

Complications. Transient ischaemic attacks; cerebral haemorrhage; cardiac arrhythmias; hyperthermia leading to disseminated intravascular coagulation, cerebral oedema and rhabdomyolysis with acute renal failure; acute psychosis—paranoia, hallucinations and aggressive behaviour.

Differential diagnosis is from other conditions causing hypoxia, seizures, or both. The clinical picture may mimic neuroleptic malignant syndrome or acute withdrawal from sedative or hypnotic drugs

TABLE II. *Summary of pharmacology of antidepressant drugs*

Drug	Comment
Tricyclics	
Amitriptylene	Anticholinergic
Imipramine	Alpha-adrenergic agonist Life-threatening cardiotoxicity
Lofepramine	Cardiotoxic in mild overdose
Tetracyclic	
Mianserine	No anticholinergic effects Less cardiotoxic than tricyclics Drowsiness is main feature
Triazolopyridine derivative	
Trazadone	Unrelated to tricyclics Toxicity is mild—drowsiness, dizziness, occasionally coma
Aralkylketone	
Fluvoxamine	Serotonin uptake inhibitor Less serious toxicity
Trifluoro-oxypropylamine derivative	
Fluoxetine	Plasma half-life 2–3 days Major metabolite has plasma half-life 7–9 days Wide margin of safety Toxicity—CNS agitation, convulsions, nausea and vomiting
Dibenzoxapines	
Amoxapine, loxapine	Block dopamine receptors Mild cardiotoxicity High incidence of convulsions Rhabdomyolysis and acute renal failure may occur Management: Aggressive anticonvulsant therapy, early intubation. Diazepam ineffective in controlling seizures

or ethanol. Other drugs which may result in a similar presentation include the hallucinogens and anticholinergics.

General management. It is essential to exclude medical causes for agitation—for example hypoxia from pneumonia, meningitis or septicaemia.

The most important aspect of care is to control the psychomotor agitation and hence to prevent complications. Place in a single room where close monitoring is possible, but where intrusion is minimal.

Check oxygen saturation, ECG, core temperature and capillary blood glucose. Commence i.v. fluids and ensure intravascular volume repletion. Give Parentrovite ampoules 1 and 2 i.v. Cool by surface cooling if core temperature > 40 °C.

Indications for tracheal intubation and artificial ventilation: uncontrollable hyperthermia; extreme agitation with danger of aspiration; uncontrollable convulsions; deep coma with danger of aspiration.

Sedation. Sedate with diazepam i.v. until agitation and seizures stop. If the required dose causes respiratory depression, tracheal intubation and artificial ventilation may be necessary. Continue regular doses of diazepam—for example 10 mg 4–6 hourly.

Other medications. Do not use neuroleptic agents. Beta-adrenergic antagonists should be avoided unless the patient is heavily sedated, because this may lead to increased alpha-adrenergic activity and increasing hypertension.

Management of cardiac arrhythmias and hypertension. Supraventricular tachycardias are common and are often caused by hyperthermia and agitation, requiring no specific antiarrhythmic therapy.

Ventricular tachyarrhythmias should be treated appropriately, the patient sedated and the lungs ventilated artificially. Lignocaine may be considered as a temporary measure, and alpha–beta-block (labetalol) or beta-block (atenolol or propranolol) may be used when the patient is undergoing artificial ventilation.

Severe hypertension which has failed to respond to sedation and artificial ventilation should be treated with vasodilators such as labetalol, or sodium nitroprusside by i.v. infusion.

Treatment of rhabdomyolysis. Rhabdomyolysis is generally associated with severe muscle pain and contractures, and is frequently complicated by acute renal failure (ARF) which may require dialysis. The management of acute rhabdomyolysis has been discussed earlier in this review.

Additional investigations. Check concentrations of serum creatine phosphokinase and urine myoglobin; perform blood and urine drug screen (including alcohol); a computed tomography scan is advisable in order to exclude complicating intercerebral pathology; blood and urine cultures.

Amphetamines and MDMA (Ecstacy)

Amphetamines may be injected, inhaled or taken orally.

Pharmacology: Methyl amphetamine (ice) is available as crystals and is smoked. It is 20 times as potent as amphetamine sulphate, with effects which are similar. 3,4-Methylene dioxymethamphetamine (MDMA) has fewer side effects in the usual dose of 200 mg taken orally, but sudden death from ventricular fibrillation has been reported.

Presentation is similar to that following intoxication with cocaine.

Management. Similar to management of cocaine intoxication. Clearance of amphetamine is increased by urinary acidification, but this should be avoided in the presence of rhabdomyolysis.

Heroin (diamorphine)

Heroin deaths are caused generally by respiratory depression with or without pulmonary aspiration. This may occur with first use, change in drug access (variability in purity) or loss of tolerance after a period of abstinence.

Presentation: coma, with slow ventilatory frequency (terminating in apnoea); pinpoint pupils (not present in pethidine intoxication).

Diagnosis. Classically, a temporary reversal of coma and respiratory depression is achieved with naloxone 0.8–2 mg i.v. Antagonism may require larger doses of naloxone if the intoxication is caused by pethidine, buprenorphine, or dextropropoxyphene, and may be suppressed by the presence of other drugs.

Treatment. Some authors suggest the use of i.v. naloxone to maintain antagonism. In our opinion, this requires very careful titration, and we consider it safer to intubate the trachea and ventilate the lungs until the intoxicant effect has worn off spontaneously.

Complications include pulmonary aspiration, noncardiogenic pulmonary oedema, rhabdomyolysis and infective complications in i.v. drug abusers.

Drug couriers. "Body packers" as they are termed, smuggle drugs by concealment in and around the body. Should the drug be swallowed in a container (e.g. condom, plastic bag or vial), leakage may lead to severe toxicity. A recent plane journey may be an indication for an abdominal x-ray. Surgical removal from the bowel may be indicated.

Psychoactive Drugs

Pharmacology. The antidepressant agents have differing activities, summarized in table II.

Tricyclic intoxication

Presentation. Cardiovascular and neurological features dominate the clinical picture.

Cardiac: hypotension; cardiac arrhythmias (ventricular and atrial); ECG abnormalities (PR, QRS and QTc prolongation). A right bundle branch block pattern is characteristic [3]. With QRS > 0.1 s, convulsions are likely; QRS > 0.16 s, ventricular arrhythmias are likely. Terminally, refractory hypotension may occur, leading to electromechanical dissociation (EMD).

CNS: convulsions; agitation, hallucinations; coma and respiratory depression.

General management. In any patient with evidence of a cardiac arrhythmia, twitching or respiratory depression, the trachea should be intubated and the lungs ventilated. Therefore, in the majority of severe intoxications, even if the patient is still conscious, he/she should undergo elective ventilation.

This management is recommended because respiratory depression, hypercapnia and hypoxia often precipitate cardiac arrhythmias; acidosis, whether respiratory or metabolic, enhances cardiotoxicity; and intubation of the trachea and ventilation of the lungs ensure preservation of the airway and safe use of anticonvulsants (e.g. benzodiazepines) which are less negatively inotropic than phenytoin.

Management of myocardial depression and arrhythmias. With good oxygenation and maintenance of pH > 7.4, cardiac arrhythmias usually resolve. Small incremental doses of sodium bicarbonate 50 mmol should be used to maintain pH > 7.4 if hyperventilation fails to achieve that goal. EMD may be precipitated by the administration of negatively inotropic agents; these should be avoided unless the arrhythmia is so bizarre that the cardiac output is not being maintained. Sodium bicarbonate 50 mmol i.v. may be effective, but if this fails, small incremental doses of lignocaine are probably the safest treatment.

Inotropes may be required, and dobutamine is suitable. Invasive haemodynamic monitoring with a pulmonary artery catheter is tempting, but should be avoided because insertion of the catheter during the acute early phase may precipitate a dangerous arrhythmia. Whilst d.c. shock may be used, it may precipitate asystole or EMD. The joule dosage should be kept to a minimum.

Physostigmine is *not* recommended.

Cardiac toxicity generally resolves within 6 h, and artificial ventilation for control of convulsions is rarely indicated after 24 h.

Monoamine Oxidase Inhibitors

Pharmacology. Overdose of these drugs alone does not produce any serious effects. Severe toxicity may occur when they are taken together with foodstuffs or drugs contraindicated during their use (e.g. foods containing precursors of biogenic amines such as tyramine, or drugs such as tyramine, sympathomimetic amines or amphetamine).

Presentation. Symptoms develop progressively over 12–24 h and include: muscle twitching, leading to diffuse muscle spasm, trismus and opisthotonos; fluctuations in arterial pressure with tachycardia; fixed, dilated pupils; hot sweaty peripheries and increased core temperature.

Complications include rhabdomyolysis, acute renal failure and disseminated intravascular coagulopathy.

Management. Control of core temperature > 39 °C by sedation, paralysis and cooling. Control of haemodynamic state, with invasive monitoring as required.

Antipsychotic Drugs

Pharmacology. These are the phenothiazine derivatives and may be grouped according to their dominant effects:

Group 1 (e.g. chlorpromazine): characterized by pronounced sedative effects and moderate anticholinergic and extrapyramidal effects.

Group 2 (e.g. thioridazine): characterized by moderate sedative effects, marked anticholinergic effects and fewer extrapyramidal effects than groups 1 or 3.

Group 3 (e.g. perphenazine): characterized by fewer sedative effects and anticholinergic effects, but more pronounced extrapyramidal effects than groups 1 and 2.

Presentation. Clinical features may include: respiratory depression; cardiac arrhythmias (the ECG may show a prolonged QT interval); sudden death (probably as a result of torsades de pointes); dystonia (generally relieved by procyclidine 5–10 mg i.v.); coma and convulsions; hypothermia; neuroleptic malignant syndrome (confusion, muscle pain and rigidity, rhabdomyolysis, fever).

General management: supportive care; maintain pH > 7.4; ensure a normal serum potassium concentration.

Management of torsades de pointes: d.c. shock and cardiac pacing 20 beat min^{-1} greater than the patient's sinus rhythm; infusion of isoprenaline 2–6 µg min^{-1} may be tried whilst pacing is established.

Sedative and Hypnotic Agents

Benzodiazepine overdosage

Death is caused by respiratory depression and aspiration of vomitus, but note that these drugs are often taken in combination with other drugs, resulting in a confusing clinical picture.

In our opinion, flumazenil should not be used for treatment because it may precipitate convulsions or acute withdrawal syndromes, and it has a short half-life (1–2 h), making repetitive doses and continued monitoring necessary.

Management: supportive care with intubation and ventilation if required.

Carbon monoxide poisoning

In England and Wales, approximately 1000 people die every year from carbon monoxide poisoning. Most of these patients do not reach hospital. Common sources of carbon monoxide are car exhaust fumes, improperly maintained and ventilated heating systems, smoke from fires, and household gas.

Pharmacology. Carbon monoxide has an affinity for haemoglobin which is 200–250 times that of oxygen. Carbon monoxide combines with haemoglobin to form carboxyhaemoglobin, and the affinity for oxygen of the remaining haem is increased. Carbon monoxide toxicity is caused by cellular anoxia, and possibly also inhibition of cellular respiration as a result of binding to other haem proteins. The elimination half-life of carbon monoxide is reduced from 250 min when the subject is breathing air, to 59 min breathing 100% oxygen, and is reduced further to 22 min when 100% oxygen is breathed at 2.2 atm.

The severity of poisoning depends on the concentration of carbon monoxide in the air, the duration of exposure and the person's general health.

Presentation. Repeated exposure: headache; fatigue; poor memory and concentration; dizziness and paraesthesia; visual disturbances; chest pain; diarrhoea and abdominal pain.

Acute exposure: carboxyhaemoglobin $< 10\%$—generally no symptoms; carboxyhaemoglobin $> 60\%$—coma, leading to cardiorespiratory arrest.

Late sequelae may include neuropsychiatric sequelae which may develop weeks after exposure (memory loss, impaired intellect, signs of cerebellar and mid-brain damage).

Signs of poisoning include: cherry red skin, coma, hyper-reflexia, convulsions and cardiac arrhythmias.

General management. Remove from site; administer 100% oxygen via tight fitting face mask (where there is respiratory depression or difficulty with airway control, intubate the trachea and ventilate the lungs with 100% oxygen); in cases of severe poisoning, assume cerebral oedema and treat accordingly.

Indications for hyperbaric oxygen therapy include: a conscious patient with a carboxyhaemoglobin $> 20\%$; depressed level of consciousness, but able to maintain airway; recovery of consciousness after an initial carboxyhaemoglobin $> 40\%$.

Contraindications to hyperbaric oxygen therapy via a single person chamber include: artificial ventilation; inability to maintain an airway; hypovolaemia or dependence on cardiac inotropes; cardiac arrhythmias potentially requiring urgent intervention; asthma.

These contraindications arise because of the practical difficulties of managing such patients in single person hyperbaric oxygen chambers, and the limited availability of compressed air chambers in which medical attendants can also be pressurized. All patients fulfilling the indications for hyperbaric oxygen therapy should be discussed with the regional hyperbaric oxygen facility. (The availability of hyperbaric oxygen facilities may be ascertained by contacting the Diving Diseases Research Centre, who provide a 24-h service. Tel.: 0752-261-910.)

Lithium intoxication

Pharmacology. This metal is eliminated by the kidney, therefore renal failure may lead to accumulation. Other circumstances which may lead to toxicity when lithium is being used for treatment include dehydration and concomitant administration of non-steroidal anti-inflammatory agents or diuretics.

Presentation. Neurological: confusion, agitation; hyper-reflexia, hypertonia, tremor; ataxia; convulsions.

Gastrointestinal: vomiting.

Metabolic: hyponatraemia; diabetes insipidus; renal failure.

The therapeutic range in blood is lithium 1.0–1.4 mmol litre^{-1}. In acute poisoning the lithium concentration is generally > 5.0 mmol litre^{-1}.

General management: gastric lavage up to 4 h after ingestion; forced diuresis. In the presence of neurological symptoms, renal failure, or both, haemodialysis should be performed.

APPENDIX

OTHER POISONINGS

Space does not allow for details about other poisons. Readers are referred to the following texts for further information on the management of specific poisons:

Alcohols and ethylene glycol

Buckley BM, Vale JA. Poisoning by alcohols and ethylene glycol. *Prescribers' Journal* 1986; **26**: 109–114.

Galliot M, Astier A, Vu Bien D, Garnier R, Likforman J, Bismuth C. Treatment of ethylene glycol poisoning with intravenous 4-methylpyrazole. *New England Journal of Medicine* 1988; **319**: 97–100.

Anticonvulsants

Dupuis RE, Lichtman SN, Pollack GM. Acute valproic acid overdose—clinical course and pharmacokinetic disruption of vaproic acid metabolites. *Drug Safety* 1990; 5: 65–71.
Henry JA. Anticonvulsants. *Care of the Critically Ill* 1991; 7: 102.
Mauro LS, Mauro VF, Brown DL, Somani P. Enhancement of phenytoin elimination by multiple dose activated charcoal. *Annals of Emergency Medicine* 1987; **16**: 1132.

Beta-2 agonists and theophylline poisoning

Vale JA. Poisoning with respiratory drugs. *Prescribers' Journal* 1986; **26**: 107–110.

Cardiac drugs

Martiny SS, Phelps SJ, Maney KL. Treatment of severe digitalis intoxication with digoxin-specific antibody fragments: a clinical review. *Critical Care Medicine* 1988; **27**: 21–56.

Chloroquine poisoning

Riou B, Barriot P, Rimailho A, Baud FJ. Treatment of severe chloroquine poisoning. *New England Journal of Medicine* 1988; **318**: 1–6.
Consensus Committee, Société de Réanimation de Langue Française. Treatment of Acute Chloroquine Poisoning. *Intensive and Critical Care Digest* 1992; **11**: 5.

Inhalation agents as poisons

Blain PG. Sulphur mustard and nerve agents, organophosphorus poisonings—chemical warfare agents. *Care of the Critically Ill* 1991; 7: 91–96.

Mushroom poisoning

Editorial. Death-cap poisoning. *Lancet* 1972; **1**: 1320–1321.
Langer M, Verconi S, Constantino D. In: Vincent JL, ed. *Update in Intensive Care and Emergency Medicine*. Berlin: Springer-Verlag, 1990; 482–493.

Paraquat poisoning

Volans GN, Byatt GM. Poisoning from domestic products. *Prescribers' Journal* 1986; **26**: 92–93.

Quinine intoxication

Proudfoot AT. Acute poisoning: an update. Current problem—quinine. *Prescribers' Journal* 1986; **26**: 80–82.

Solvents

Flanagan RJ, Ruprah M, Meredith TJ, Ramsay JD. An introduction to the clinical toxicology of volatile substances. *Drug Safety* 1990; 5: 359–383.
Henry JA. Volatile substance abuse. *Care of the Critically Ill* 1991; 7: 105.

REFERENCES

1. Abuelo JG. Renal failure caused by chemicals, foods, plants, animal venoms, and misuse of drugs. An overview. *Archives of Internal Medicine* 1990; **150**: 505–510.
2. Ashton CH. Benzodiazepine overdose: are specific antagonists useful? *British Medical Journal* 1985; **290**: 805–806.
3. Boehert MT, Lovejoy FH. Value of the QRS duration *versus* the serum drug level in predicting seizures and ventricular
7. Flanagan RJ, Huggett A, Saynor DA, Raper SM, Volans GN. Value of toxicological investigation in the diagnosis of acute drug poisoning in children. *Lancet* 1981; **2**: 682–685.
8. Fuller GN, Rea AJ, Payne JF, Lant AF. Parasuicide in central London 1984–1988. *Journal of the Royal Society of Medicine* 1989; **82**: 653–656.
9. Harsch HH. Aspiration of activated charcoal. *New England Journal of Medicine* 1986; **314**: 318.
10. Helliwell M, Hampel G, Sinclair E, Huggett A, Flanagan RJ. Value of emergency toxicological investigations in differential diagnosis of coma. *British Medical Journal* 1979; **2**: 819–821.
11. Henry J, Volans G. ABC of Poisoning – Diagnosis. *British Medical Journal* 1984; **289**: 172–174.
12. Henry J, Volans G. ABC of poisoning. Preventing Absorption. *British Medical Journal* 1984; **289**: 304–305.
13. Ilett KF, Gibb SM, Unsworth RW. Syrup of ipecacuanha as an emetic in adults. *Medical Journal of Australia* 1977; **2**: 91–93.
14. Keays R, Harrison PM, Wendon JA, Forbes A, Gove C, Allexander GJM, Williams R. Intravenous acetylcysteine in paracetamol-induced hepatic failure: a prospective controlled trial. *British Medical Journal* 1991; **303**: 1026–1029.
15. Keays R, Williams R. Paracetamol poisoning and liver failure. *Prescribers' Journal* 1989; **29**: 155–162.
16. Kirshenbaum LA, Mathews SC, Sitar DS, Tenenbein M. Does multiple-dose charcoal therapy enhance salicylate excretion? *Archives of Internal Medicine* 1990; **150**: 1281–1283.
17. Lheureux P, Even-Adin D, Askenasi R. Current status of antidotal therapies in acute human intoxications. *Acta Clinica Belgica Supplementum* 1990; **13**: 29–47.
18. Levy G. Gastrointestinal clearance of drugs with activated charcoal. *New England Journal of Medicine* 1982; **307**: 676–678.
19. Levy G, Houston JB. Effect of activated charcoal on acetaminophen absorption. *Pediatrics* 1976; **58**: 432–435.
20. Levy G, Tsuchiya T. Effect of activated charcoal on aspirin absorption in man. Part 1. *Clinical Pharmacology and Therapeutics* 1972; **13**: 317–322.
21. Leykin Y, Halpern P, Silbiger A, Sorkin P, Niv D, Rudick V, Geller E. Acute poisoning treated in the intensive care unit: A case series. *Israel Journal of Medical Sciences* 1989; **25**: 98–102.
22. Locket S. Evaluation of various forms of treatment administered in poisoning. *Practitioner* 1973; **210**: 709–714.
23. Meadow R. ABC of Child Abuse – Poisoning. *British Medical Journal* 1989; **298**: 1445–1446.
24. Menzies DG, Busuttil A, Prescott LF. Fatal pulmonary aspiration of oral activated charcoal. *British Medical Journal* 1988; **297**: 459–460.
25. Merigian KS, Woodard M, Hedges JR, Roberts JR, Stuebing R, Rashkin MC. Prospective evaluation of gastric emptying in the self poisoned patient. *American Journal of Emergency Medicine* 1990; **8**: 479–483.
26. Meulemans A, Van den Berghe G, Delooz WH. Gastro-intestinal decontamination for acute poisoning. *Acta Clinica Belgica Supplementum* 1990; **13**: 13–19.
27. Nejman G, Hoekstra J, Kelly M. Journal Club: Gastric emptying in the poisoned patient. *American Journal of Emergency Medicine* 1990; **8**: 265–269.
28. Neuvonen PJ, Vartiainen M, Tokola O. Comparison of activated charcoal and ipecac syrup in prevention of drug absorption. *European Journal of Clinical Pharmacology* 1983; **24**: 557–562.
29. Office of Population Censuses and Surveys. *Mortality Statistics for England and Wales 1990*. London: HMSO, 1991 (DH 2 series No. 17).

[redacted]

Eliminating poisons. *British Medical Journal* 1984; **289**: 366–369.

35. Vale JA, Meredith TJ, Proudfoot AT. Syrup of ipecacuanha: is it really useful? *British Medical Journal* 1986; **293**: 1321–1322.
36. Watson WA, Cremer KF, Chapman JA. Gastrointestinal obstruction associated with multiple-dose charcoal. *Journal of Emergency Medicine* 1986; **4**: 401–407.
37. Wheeler-Usher DH, Wanke LA, Bayer MJ. Gastric emptying. Risk versus benefit in the treatment of acute poisoning. *Medical Toxicology* 1986; **1**: 142–153.
38. Winchester JF, Gelffand MC. Hemoperfusion in drug intoxication: clinical and laboratory aspects. *Drug Metabolism Reviews* 1978; **8**: 69–104.
39. Wright N. An assessment of the unreliability of the history given by self-poisoned patients. *Clinical Toxicology* 1980; **16**: 381–384.

British Journal of Anaesthesia 1993; **70**: 574–575

SHORT COMMUNICATIONS

EFFECT OF AGE ON THE SENSITIVITY OF UPPER AIRWAY REFLEXES

R. J. ERSKINE, P. J. MURPHY, J. A. LANGTON AND G. SMITH

SUMMARY

We have recorded the threshold concentration of inhaled ammonia vapour required to elicit reflex glottic closure (NH_3TR) in 102 healthy, non-smoking volunteers (39 female) aged 17–96 yr in order to assess the effect of age upon upper airway reflex sensitivity. A single measurement of sensitivity was made in each subject using a system delivering small concentrations of ammonia vapour for single intermittent breaths to the upper airway and recording glottic closure using an inspiratory pneumotachograph. We found a strong positive correlation between age and NH_3TR, indicating a decrease in upper airway reflex sensitivity with increasing age. (Br. J. Anaesth. 1993; **70**: 574–575)

KEY WORDS

Age factors. Airway: reflex sensitivity.

Reflex activity is thought to diminish with advancing age. Laryngeal reflexes in the elderly appear to be less active, both during induction of anaesthesia and in the recovery room, compared with the younger patient—suggesting that protection of the airway may be impaired in the elderly [1].

The protective reflex of the larynx is evoked by stimulation of receptors thought to be located in the hypopharynx and larynx. With concentrations of irritant vapour smaller than that required to produce cough, the response is glottic closure, and a brief pause in inspiration. The upper airway is sensitive to both chemical and mechanical stimuli, the former being both quantifiable and reproducible [2].

Using equipment described previously [2], we have measured the threshold concentration of ammonia vapour (NH_3TR) required to stimulate reflex glottic closure in patients. Previous workers [3] found a six-fold increase in the concentration of inhaled ammonia vapour required to produce a reflex stop in inspiration in patients between the second and eighth and ninth decades. However, that study population contained a large proportion of smokers and our early work [4] has shown that smokers have considerably more sensitive upper airway reflexes than non-smokers.

The aim of this study was to measure NH_3TR in non-smokers over a broad age range in order to assess the effect of age alone on upper airway reflex sensitivity.

METHODS AND RESULTS

After obtaining Ethics Committee approval and informed subject consent, we studied 102 healthy, non-smoking subjects aged 17–96 yr. The majority (85) were preoperative elective surgical patients, the remainder being members of our department, nursing staff and nine patients from geriatric wards. We excluded those with mental or neurological impairment, chronic bronchitis and asthma, a history of upper respiratory tract infection in the past month, and those receiving sedative medication. Two subjects had smoked in the past: one stopped 25 yr previously, the other stopped 4 weeks before the study.

Measurements were made either in our laboratory or on the ward, using the same portable equipment. A single measurement of NH_3TR was made in each subject, using the method described previously [2]. We have found that no significant difference exists between repeated measures made on the same day and on separate days in the same individual [2].

NH_3TR was plotted against age for each subject (fig. 1); there was an increase in NH_3TR with advancing age. The correlation coefficient was calculated as +0.85, indicating a strong positive correlation between age and NH_3TR.

Mean NH_3TR for the age group 21–30 yr ($n = 14$) was 571 (SEM 41.5) p.p.m., compared with a value of 1791 (52) p.p.m. for the group aged 86–95 yr ($n = 14$).

COMMENT

Whilst loss of peripheral reflexes in the elderly may be of little anaesthetic significance, the reduction in the sensitivity of upper airway reflexes associated with age may be important, particularly after anaesthesia or sedation, when full airway protection may be delayed, with a consequent increased risk of aspiration [1].

In 1960, Pontoppidan and Beecher carried out a similar study using ammonia vapour [3]. They

---

R. J. ERSKINE*, F.R.C.ANAES.; P. J. MURPHY, F.R.C.ANAES.; J. A. LANGTON, F.R.C.ANAES.; G. SMITH, B.SC., M.D., F.R.C.ANAES.; University Department of Anaesthesia, Leicester Royal Infirmary, Leicester LE1 5WW. Accepted for Publication: November 25, 1992.

*Present address, for correspondence: Department of Anaesthesia, University Hospital, Queens Medical Centre, Nottingham NG7 2UH.

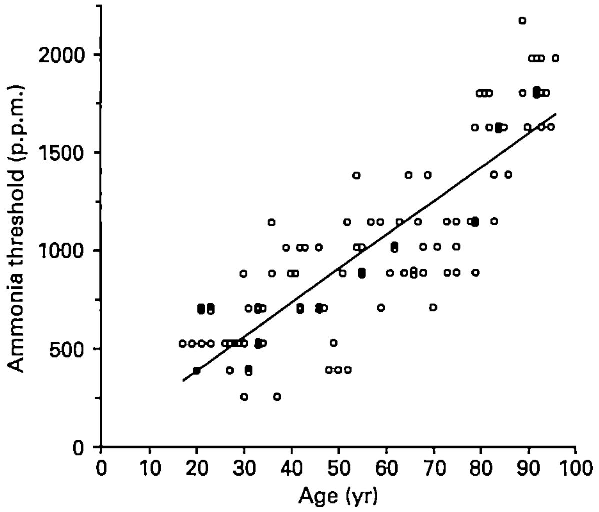


FIG. 1. Correlation between age and ammonia threshold. Regression equation: $y = 17.1x + 43.4$; correlation coefficient: $+0.85$.

assessed 103 subjects aged 15–84 yr and found that the threshold increased more than six-fold from the second to the eighth and ninth decades, and that the between-subject variability in sensitivity increased with age. However, we have identified several factors that may have produced inaccuracies.

First, their breathing system contained a large canister into which the ammonia vapour was injected. This could have allowed streaming to occur and, depending upon inspiratory flow and the timing of inspiration, could have produced a variable concentration of ammonia. Also, depending upon the tidal volume and inspiratory flow rate of the subject, the stimulus may have been presented to the upper airway at differing times during the ventilatory cycle. The authors stated that the actual concentration of inhaled ammonia was unknown, but was assumed to be directly proportional to the absolute amount of ammonia used. Furthermore, seven subjects failed to respond to the maximum delivered stimulus of ammonia. Second, they used a metabolic spirometer to record the change in inspiratory flow, and not a pneumotachograph. Finally, their population contained a high proportion of smokers (85 %), although this varied between 33 % in the 70–79 yr group and 83 % in the 50–59 yr group, but they could find no consistent influence of smoking upon airway irritability. In contrast, we have found that those subjects who regularly smoke more than 15 cigarettes per day have a significantly smaller NH_3TR than non-smokers of the same age [4], indicating that smokers have more sensitive upper airway reflexes. Therefore, in this study we have excluded smokers.

In essence, our results support Pontoppidan and Beecher's work, indicating an increase in NH_3TR with increasing age, but we found the mean NH_3TR increased only three-fold from the third to the ninth and tenth decades—a change which was only 50 % of that of their study. In addition, we found no increase in between subject variability in NH_3TR with age and, in general, our results were more tightly clustered in each age group. These differences between the earlier study and ours, in particular regarding distinction between smokers and non-smokers, may be explained by the improved design of our system, which delivers a more constant, known concentration of ammonia vapour [2].

The cause of this increased threshold in the elderly is unknown. The irritant receptors in the upper airway are thought to consist of free nerve endings ramifying among epithelial cells; they have been classified as type 1, rapidly adapting receptors, although no nervous end-organ has been identified histologically. Increasing age is associated with a reduction in the population of nerve endings and this, combined with the thickening that occurs in the mucosa of the upper airway thus reducing penetration of noxious chemicals, may lead to an increase in stimulation threshold. A decrease in amplitude of electrical potentials in pulmonary afferent vagal fibres with age (possibly caused by degenerative changes in sensory neurones of the Nodose (Vagal) ganglion) has been described in humans [5]. A similar mechanism may affect fibres from the superior laryngeal nerve. A histological study of age-related changes in the rat superior laryngeal nerve has demonstrated segmental demyelination and axonal degeneration in the elderly group and other ultrastructural changes associated with complete fibre dysfunction [6]. Several of these changes resemble those seen in aged human peripheral nerves, in which a decrease in fibre numbers is also a significant feature [5].

It is not possible to infer directly from our results that a progressively greater NH_3TR associated with advancing age implies a loss of protective reflexes and consequent increased risk of aspiration. However, the increased reflex stimulus threshold in the elderly may be a contributory factor, and emphasizes the need for increased vigilance during recovery from anaesthesia or sedation.

ACKNOWLEDGEMENTS

This study was supported by a grant from the Trent Regional Health Authority and an equipment grant from The Association of Anaesthetists of Great Britain and Ireland.

REFERENCES

1. Davenport HT. Anaesthesia for the geriatric patient. *Canadian Anaesthetists Society Journal* 1983; **30**: S51–S55.
2. Langton JA, Murphy PJ, Barker P, Key A, Smith G. Measurement of the sensitivity of upper airway reflexes. *British Journal of Anaesthesia* 1993; **70**: 126–130.
3. Pontoppidan H, Beecher HK. Progressive loss of protective reflexes in the airway with the advance of age. *Journal of the American Medical Association* 1960; **174**: 2209–2213.
4. Erskine RJ, Murphy PJ, Langton JA, Smith G. Upper airway reactivity in smokers and non-smokers. *Tenth World Congress of Anaesthesiologists 1992*, The Hague, Holland. Abstract 197.
5. Brizzee KR, Ordy JM. Effects of age on visceral afferent components of the autonomic nervous system. In: Brizzee KR, Ordy JM, eds. *Sensory Systems and Communication in the Elderly*, *Aging*, Vol. 10. New York: Raven Press, 1979; 58–59.
6. Rosenberg SI, Malmgren LT, Woo P. Age-related changes in the internal branch of the rat superior laryngeal nerve. *Archives of Otolaryngology Head and Neck Surgery* 1989; **115**: 78–86.

British Journal of Anaesthesia 1993; **70**: 576–578

ENDOBRONCHIAL CUFF PRESSURES

M. COBLEY, J. F. KIDD, B. A. WILLIS AND R. S. VAUGHAN

SUMMARY

In 20 adult patients (18 male) who presented for thoracotomy, the trachea was intubated using Mallinckrodt disposable double-lumen tubes (18 large and two medium). The endobronchial cuff was inflated by a trained operating department assistant using an air-filled syringe. The volume of air and the initial endobronchial cuff pressure were measured. The minimum cuff pressure required to prevent respiratory gas leakage from the isolated lung was measured also and maintained using the Cardiff Cuff Controller. Mean initial cuff pressure was 69.3 (SEM 6.0) mm Hg, whereas the mean minimum cuff pressure was 29.5 (4.0) mm Hg (P < 0.0001). The results suggest that the method described of inflating the endobronchial cuff may lead to overinflation and subsequent excessive pressure on the endobronchial wall. (Br. J. Anaesth. 1993; **70**: 576–578)

KEY WORDS

Equipment: double lumen tubes, endobronchial cuff pressures.

The inflatable cuff of the endobronchial limb of the double-lumen tube has two functions. It allows independent positive pressure ventilation of the one lung and also selectively isolates the other lung. It is recognized that excessive cuff pressure exerted on the tracheal wall is associated with trauma [1]. To minimize these problems, high volume low pressure cuffs and an electropneumatic instrument for measuring and controlling cuff pressures have been devised [2].

Tracheal rupture may be produced by tracheal tubes. Incidents of bronchial rupture have also been reported, but are rarer and have been associated with the use of the older and stiffer high pressure cuffs of the Robertshaw [3] and Carlens [4] types.

Rapid inflation of the endobronchial cuff is thought to be the cause of bronchial rupture [3, 4]. Measurement of tracheal cuff pressure is performed rarely in clinical practice, but an earlier study by Willis, Latto and Dyson [5] showed that such measurements can prevent accidental overinflation of the tracheal cuff. Furthermore, the use of the Cardiff Cuff Controller allows the clinician to maintain the cuff at a predetermined pressure—ideally, the minimum necessary to prevent leakage. It seems reasonable to suppose that the endobronchial cuff is also susceptible to accidental overinflation.

The aim of this study was two-fold: first to measure the initial endobronchial cuff pressure (ECPi) produced by syringe inflation, performed under normal clinical conditions by a trained operating department assistant; second to measure the pressure, in the same endobronchial cuff, which just prevented leakage of gas from the isolated lung, but using the Cardiff Cuff Controller rather than syringe inflation. This pressure was deemed the minimum endobronchial cuff pressure (ECPmin).

METHOD AND RESULTS

Two instruments were used to measure pressure. The first measured ECPi and was a portable, electrically powered pressure transducer with a built-in amplifier and digital display. The transducer possessed a low compliance with a small internal volume (150 µl) which allowed measurement of the pressure within an inflated cuff by connecting the cuff pilot balloon directly to the transducer. The transducer response was linear over the range 0–200 mm Hg, and a built-in reference voltage permitted calibration.

The Cardiff Cuff Controller was used to measure and maintain ECPmin. This instrument is an electropneumatic device which incorporates the same pressure transducer for measurement, but has the additional facility to maintain a constant cuff pressure at a preset value in the range 5–150 mm Hg, to within 1 mm Hg.

We studied 20 patients (18 male) undergoing elective thoracotomy. Their mean age, height and weight were 56.3 (SEM 2.5) yr, 169 (SEM 1.7) cm and 69.3 (SEM 2.4) kg, respectively. After induction of anaesthesia and neuromuscular block, the lungs were ventilated with 66 % nitrous oxide and 1 % enflurane

TABLE I. *Initial (ECPi) and minimum (ECPmin) endobronchial cuff pressures and the volume of air (Volume) which produced ECPi (mean (SEM)) in 20 patients.* ***P < 0.0001 *(Student's paired t test; 19 d.f.)*

ECPi (mm Hg)	Volume (ml)	ECPmin (mm Hg)	ECPi − ECPmin (mm Hg)
69.3 (6.0)	2.3 (0.2)	29.5 (4.0)	39.8 (6.5)***

M. COBLEY, F.R.C.ANAES.; J. F. KIDD, F.R.C.ANAES.; B. A. WILLIS, PH.D., F.R.C.ANAES.; R. S. VAUGHAN, F.R.C.ANAES.; Department of Anaesthetics, University Hospital of Wales, Heath Park, Cardiff CF4 4XW. Accepted for Publication: December 7, 1992.

Correspondence to M. C.

in oxygen. A right- or left-sided, double-lumen, disposable, Mallinckrodt endobronchial tube with high volume and low pressure cuffs was inserted and positioned accordingly. These tubes are manufactured in three sizes, large, medium or small. The large size was used for all male patients (18) and a medium size for females (two). Seventeen tubes were left-sided and three right-sided; all the right sided tubes were placed in male patients.

A three-way tap was connected to the pilot balloon of the endobronchial cuff and the cuff was inflated carefully by a trained operating department assistant using a 5-ml, air-filled syringe via this tap. The air was injected in small increments of 0.5 ml until no discernible leak was detected by the anaesthetist. Assessment of the presence of leak past the endobronchial cuff, at a standardized inflation pressure of 25 cm H_2O, was achieved by auscultation of both sides of the chest during one-lung ventilation, with only the bronchial cuff inflated. The lung port of the non-dependent, unventilated lung was open to atmosphere and helped to determine any leak past the bronchial cuff by noting the presence or absence of expired gases. If, during the incremental injection of air, resistance to injection was felt, the final 0.5-ml increment was decreased carefully until no leak was detectable as assessed by our method. The final volume of air injected was noted. The three-way tap was connected to the pressure transducer and ECPi measured.

The investigators consider this method of endobronchial cuff inflation to be the technique practised most commonly. Although great care is exercised not to over inflate the cuff, we suspect that the obvious lack of sensitivity of this method may inadvertently produce overinflation of the endobronchial cuff.

Subsequently, the three-way tap was attached to the Cardiff Cuff Controller and the pressure in the cuff (ECPi) was modified precisely until the cuff pressure was just sufficient to prevent gas leakage from the isolated lung as detected by auscultation, in the same manner as described earlier and at the same inflation pressure. At this point, the new cuff pressure (ECPmin) was noted. The cuff was maintained at this preset pressure for the duration of the operation. Any leak that occurred during the procedure was noted and the new cuff pressure necessary to prevent leakage was recorded. This pressure was maintained for the remainder of the operation. The mean duration of operation was 3 (SEM 0.1) h.

In addition, *in vitro* endobronchial cuff pressure *vs* volume curves were plotted for the double-lumen tubes used.

The mean pressures and the volumes of air injected into the cuff to achieve the mean ECPi and the mean ECPmin are shown in table I. The overall mean ECPi was 69.3 (SEM 6.0) mm Hg, with a mean ECPi for right-sided tubes of 65.7 mm Hg and mean ECPi for left-sided tubes of 69.9 mm Hg. This compared with an overall mean ECPmin of 29.5 (SEM 4.0) mm Hg: right-sided tube mean ECPmin 24.6 mm Hg and left-sided mean ECPmin 30.32 mm Hg. Using a paired Student's t test, a significant difference was demonstrated between mean ECPi and ECPmin ($P < 0.0001$).

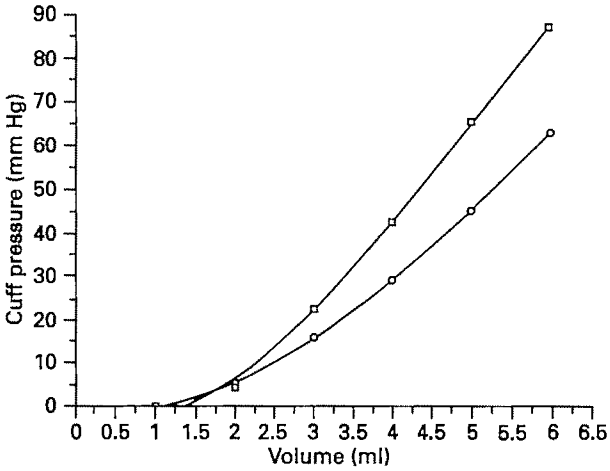


FIG. 1. Endobronchial cuff pressure produced by inflating medium (○) and large (□) double-lumen tubes with various volumes of air.

When they were inflated *in vitro* with 4 ml of air (maximum *in vivo* inflation volume) the bronchial cuff of both the large and medium size tubes had a diameter of 2.3 cm and they developed cuff pressures of 65 mm Hg and 44 mm Hg, respectively. Inflation with 2.5 ml of air (mean *in vivo* volume) produced a cuff diameter of 2.0 cm and cuff pressures of 13 mm Hg and 10 mm Hg, respectively (fig. 1). These diameters compare with the actual bronchi sizes of right bronchus (male 1.2–2.1 cm (mean 1.7 cm); female 1.1–2.0 cm (mean 1.5 cm)) and left bronchus (male 1.0–1.8 cm (mean 1.5 cm); female 0.9–1.5 cm (mean 1.2 cm)). Thus the greater cuff pressures *in vivo* are caused by pressure exerted against the bronchus.

COMMENT

The difference between manual syringe inflation of the cuff and the electropneumatic method lies in the relative lack of sensitivity of the former method. Small changes in the volume injected into the cuff result in relatively large increases in cuff pressure. The Cardiff Cuff Controller controls pressures to within 1 mm Hg and, although the end-point is the same (absence of auscultated leakage passed the cuff), the manual inflation method usually overshoots that end-point pressure. Therefore, syringe inflation, however carefully performed, clearly produces overinflation of the endobronchial cuff and this can exert an unnecessarily great pressure on the bronchial mucosa.

In the absence of an auscultated leak, aspiration is an unlikely event. However, an overinflated cuff may result in ischaemic damage to the mucosa with subsequent stenosis or, in cases of gross overinflation, bronchial rupture. The optimum pressure for a cuff is the pressure which prevents aspiration, allows leak-free ventilation and does not produce bronchial mucosal ischaemia. As the incidence of bronchial mucosal damage is not known, it is safer to maintain the bronchial cuff at that pressure which justs prevents auscultated leakage.

The tracheal cuff pressure has been shown to equal the pressure exerted on the tracheal wall with high volume, low pressure cuffs. There seems no reason to suppose that the high volume, low pressure endobronchial cuff differs. Tracheal damage is attributed to both increased lateral wall pressure and the duration of anaesthesia, with lateral wall pressure the more important factor (6). Moreover, a linear increase in cuff pressure over a 3-h period has been demonstrated when the inspired gases contain nitrous oxide. These risk factors are no less relevant when considering endobronchial cuffs. The high lateral bronchial wall pressure which may develop with overinflated cuffs can impair mucosal blood flow and thereby contribute to the risk of bronchial rupture.

To reduce the risk of inadvertent overinflation, the anaesthetist should instruct the assistant to inflate the cuff just enough to abolish a leak from the isolated lung. The temptation to add additional volume for good measure should be strongly discouraged. We have shown that careful syringe inflation alone is not necessarily enough to prevent overinflation of the cuff. The use of a cuff pressure controller such as the Cardiff Cuff Controller [2], with its greater sensitivity of control, enables cuff pressure to be set more precisely and accurately to a specific value known just to eliminate leakage. The cuff pressure can also be maintained at the chosen pressure even in the presence of nitrous oxide when significant pressure increases resulting from diffusion of nitrous oxide into the cuff have been reported.

REFERENCES

1. Seegobin RD, Van Hasselt GL. Endotracheal cuff pressure and tracheal mucosal blood flow; endoscopic studies of effects of four large volume cuffs. *British Medical Journal* 1984; **288**: 965–968.
2. Morris JV, Latto IP. An electropneumatic instrument for measuring and controlling the pressures in the cuffs of tracheal tubes: the Cardiff Cuff Controller. *Journal of Medical Engineering and Technology* 1985; **9**: 229–230.
3. Heiser MD, Steinberg MD, MacVaugh H, Klineberg MB. Bronchial rupture, a complication of use of the Robertshaw double-lumen tube. *Anesthesiology* 1979; **51**: 88.
4. Guernelli N, Bragaglia RB, Bricolli A, Mastrorilli M, Vecchi R. Tracheobronchial ruptures due to cuffed Carlens tubes. *Annals of Thoracic Surgery* 1979; **28**: 66–68.
5. Willis BA, Latto IP, Dyson A. Tracheal tube cuff pressures. *Anaesthesia* 1988; **43**: 312–314.
6. Nordin U. The trachea and cuff induced tracheal injury. An experimental study on causative factors and prevention. *Acta Otolaryngology* 1976; **345**: 1.

British Journal of Anaesthesia 1993; **70**: 579–580

LIPID SOLUBILITY OF PANCURONIUM AND VECURONIUM DETERMINED BY N-OCTANOL/WATER PARTITIONING

M. WEINDLMAYR-GOETTEL, H. GILLY, E. SIPOS AND
K. STEINBERIETHNER

SUMMARY

We have measured the n-octanol/water distribution coefficients at 37 °C of two steroidal myoneural blockers (pancuronium and vecuronium) and of their 3-hydroxy metabolites over a pH range from 1.5 to 11. Pancuronium was found not to be lipid soluble. The mean distribution coefficient of 3-hydroxy vecuronium at pH = 7.4 was 0 and that of vecuronium 0.12 (SD 0.1). Distribution coefficients of the parent drug showed a slightly greater lipid solubility than the metabolite (11.37 (2.91) and 9.53 (3.44), respectively (mean $t_{0.05} \times$ SE)). Because of its lipid solubility, vecuronium may penetrate into lipid structures. (Br. J. Anaesth. 1993; **70**: 579–580)

KEY WORDS

Biotransformation: metabolites. Neuromuscular relaxants: pancuronium, vecuronium.

The lipid solubility of a drug is of utmost importance for its disposition within the body and, in particular, for its permeation through membranes [1]. The lipid solubility of a compound is expressed in terms of its distribution coefficient between a model lipid, mostly n-octanol, and an aqueous buffer solution [1, 2]. In general, the lipid solubility of drugs used in anaesthesia, such as opioids and analgesics, has been investigated thoroughly [2]. For myoneural blockers, however, to our knowledge no quantitative data are available.

METHODS AND RESULTS

The validity of our analytical approach was verified by determining the distribution coefficients (L) of compounds with well-known, high and low lipid solubility (salicylic acid: $L = 162$, p$K = 3.0$; sulphanilic acid: $L = 0.00013$, p$K = 3.2$ [1]). Optimum conditions for the determination of distribution coefficient were evaluated in preliminary experiments. Each pH-adjusted solvent (Davis buffer [3]) was presaturated with n-octanol. The n-octanol was equilibrated with the aliquot amount of pH-adjusted reference solutions containing salicylic acid and sulphanilic acid (at room temperature) or neuromuscular blockers (at 37 °C). An equilibration period of 2 h was found to be sufficient [2].

Concentrations of salicylic acid and sulphanilic acid in the water phase were measured photometrically, the myoneural blocker was quantified by HPLC [4]. Up to 12 samples were analysed at each pH value. The distribution coefficients were calculated according to the formula given by Le Petit [3].

Data are presented as means ($t_{0.05} \times$ SE). An non-sigmoid function as deduced by Le Petit [5] was used to approximate the pH dependence of the distribution coefficient using software package Fig. P (Version 6.0 c, Software Corporation, Durham North Carolina, U.S.A.). Statistical significance was checked using the t test, assuming the level of significance to be 95% ($P < 0.05$).

The mean distribution coefficient of salicylic acid measured at pH 1.5 was 161.2 (SD 3.1). The value resulting from the curve fitting of all measurements at 25 °C was 176.52 ($t_{0.05} \times$ SE 7.44), which corresponds to the nominal value ([1]-pH not specified). The n-octanol/water distribution coefficient of sulphanilic acid was less than the detection limit of 0.02 (pH 1.5–8).

Independent of pH, the distribution coefficient of pancuronium was less than the detection limit. Pancuronium remained stable in the aqueous solution at pH values less than 8. 3-Hydroxy pancuronium could be detected only at pH > 8.0; however, the concentration of this metabolite did not exceed 5%, even at pH 11.

n-Octanol/water distribution coefficients of vecuronium in the presence of its 3-hydroxy metabolite are presented in figure 1. The data fitting yielded a partition coefficient of 11.37 ($t_{0.05} \times$ SE 2.91). Vecuronium is stable only in highly acid solutions and, when dissolved in water, it decomposes into its metabolites. At pH 7.4, about 60% and at pH 11, almost 100% of vecuronium is de-acetylated into both 3-hydroxy vecuronium (up to 85%) and 3,17-dihydroxy vecuronium (up to 15%). For this reason, the data measured represent the solubility of vecuronium/3-hydroxy vecuronium and the 3,17-dihydroxy metabolite rather than that of pure vecuronium. In figure 1 also, the results of 3-

---

MARIA WEINDLMAYR-GOETTEL, PH.D.; H. GILLY, PH.D.; E. SIPOS; Clinic of Anaesthesia and General Intensive Care Medicine (Department B), University of Vienna, Spitalgasse 23, A-1090 Vienna, Austria. K. STEINBEREITHNER, M.D., L. Boltzmann Institute of Experimental Anaesthesiology and Research in Intensive Care Medicine, Vienna, Austria. Accepted for Publication: November 11, 1992.

Correspondence to M.W.-G.

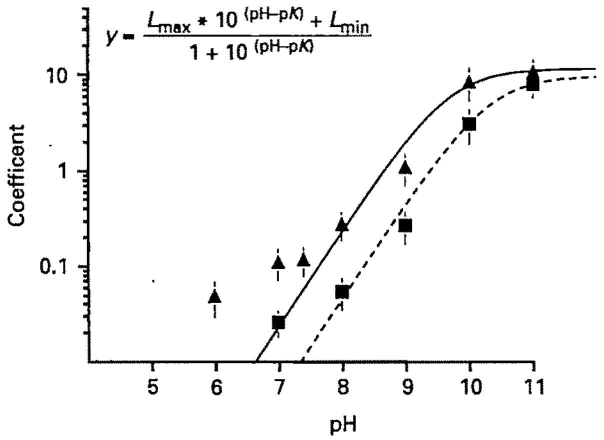


FIG. 1. Distribution coefficient (L) *vs* pH for mixture of vecuronium and its metabolite, 3-hydroxy vecuronium ($n = 95$) (▲) and for 3-hydroxy vecuronium ($n = 30$) (■) (mean ($t_{0.05} \times$ SE)). For curve fitting, all individual data were used. Resulting curve parameters were: vecuronium—$L_{max} = L_{pH\text{-}14} = 11.37$ (2.91); $L_{min} = L_{pH\text{-}0} = 0.0$ (1.10); p$K = 9.69$ (0.52). 3-Hydroxy vecuronium—$L_{max} = L_{pH\text{-}14} = 9.53$ (3.44); $L_{min} = L_{pH\text{-}0} = 0.0$ (1.07); p$K = 10.32$ (0.57).

hydroxy vecuronium are presented. At pH values greater than 7, the distribution coefficient increases, forming a characteristic curve.

COMMENT

In order to assess our analytical technique for determining lipid solubility, quality control was performed by using two reference substances, salicylic acid and sulphanilic acid. The values obtained for the n-octanol/water solubility of salicylic acid are in good agreement with the published data [1]. The distribution coefficient of sulphanilic acid—selected for its extremely low lipid solubility—is less than 0.02.

Until now, steroidal myoneural blockers as quaternary amines were considered to be insoluble in lipids [2]. It is surprising that no exact data of their distribution coefficients are given, which rules out comparison of the various myoneural blocking agents.

For all our tests we used pancuronium, vecuronium and the metabolites as pure substances (without stabilizing agents). However, when the stock solution was prepared by dissolving the pure substances in water, the pH-dependent chemical instability, especially of vecuronium, had to be taken into account. Therefore, the quantities of both the parent compound and the main metabolites were determined in each sample. We had to perform a separate test series with the object of determining the lipid solubility of this metabolite, also.

Vecuronium and 3-hydroxy vecuronium yielded similar distribution coefficients (11.36 (2.91) *vs* 9.53 (3.44)) and, as could be expected from theoretical considerations, the more polar deacetylated metabolite has a somewhat smaller distribution coefficient. Both substances appear to be lipid-soluble at pH > 8. Within the physiological pH range, however, the n-octanol/water distribution coefficient of vecuronium was significantly greater than the detection limit.

The distribution coefficient of pancuronium proved to be extremely small, hence it can be concluded that pancuronium is lipophobic. Even in the high pH range, the amount of 3-hydroxy pancuronium in the buffer solution was less than 5%; as a result its distribution coefficient was not measured.

In conclusion we state that, although the lipid solubility of vecuronium is low, it is markedly greater than that of pancuronium. When pH derangement occurs (e.g. alkalosis), penetration of vecuronium and its metabolites into lipid structures would therefore be more pronounced than that of pancuronium. Clinical consequences of this observation have not been investigated so far, but greater penetration of vecuronium than of pancuronium through the blood–brain barrier has been observed in animal experiments [6]. This may be significant in cerebral trauma or neurosurgical patients with impaired blood–brain barrier function.

REFERENCES

1. Rapoport SI. *Blood-Brain Barrier in Physiology and Medicine.* New York: Raven Press, 1976.
2. Leo A, Hansch C, Elkins D. Partition coefficients and their uses. *Chemical Reviews* 1971; 71: 525–616.
3. Le Petit G. Arbeitsvorschrift zur Bestimmung des Verteilungskoeffizienten. *Zentralblatt für Pharmazie* 1984; 123: 471–473.
4. Weindlmayr-Goettel M, Lankmayr EP, Köberl G, Gilly H. Determination of vecuronium and their metabolites in human and animal plasma using HPLC and post-column ion-pair extraction with fluorimetric detection. *Fresenius Journal of Analytical Chemistry* 1992; 343: 85–86.
5. Le Petit G. Die pH-abhängige Lipidlöslichkeit von Arzneistoffen. Mathematische Darstellung des scheinbaren Verteilungskoeffizienten. *Pharmazie* 1980; 35: 696–698.
6. Werba A, Gilly H, Weindlmayr-Goettal M, Spiss CK, Steinbereithner K. Osmotic blood–brain barrier disruption in the pig enhances penetration of pancuronium and vecuronium in cerebrospinal fluid. *Euroanaesthesia 92. Proceedings of the European Academy of Anaesthesiology* March 20–21, 1992.

British Journal of Anaesthesia 1993; **70**: 581–582

TETANIC FADE DURING RECOVERY FROM VECURONIUM BLOCK: COMPARISON OF SYSTEMIC AND ISOLATED FOREARM ADMINISTRATION

N. T. A. CAMPKIN, J. R. HOOD AND S. A. FELDMAN

SUMMARY

We have compared the degree of tetanic fade relative to twitch depression occurring after isolated forearm block with vecuronium and that after systemic i.v. injection. Fifteen patients received either vecuronium 0.3 mg into an isolated forearm or vecuronium 0.05 mg kg^{-1} systemically. Adductor pollicis mechanomyography was used to monitor recovery of twitch height at 0.2 Hz. At 25, 50, 75 and 100% recovery of twitch height, a 5-s, 50-Hz tetanus was administered and tetanic fade ratio measured. There was significantly less tetanic fade in the isolated forearm group ($P < 0.01$; unpaired t test) at 25, 50 and 75% twitch height. This suggests that twitch depression and tetanic fade are independently mediated effects of vecuronium. (Br. J. Anaesth. 1993; **70**: 581–582)

KEY WORDS

Neuromuscular relaxants: vecuronium. Neuromuscular transmission: tetanic fade.

There is considerable evidence that twitch depression and fade produced by non-depolarizing neuromuscular blocking drugs are separate effects, mediated at different sites within the neuromuscular junction [1], although this model has been questioned recently [2, 3]. Bowman and Webb [4] noted that different techniques of drug administration in cats may produce different degrees of fade relative to twitch height, suggesting that the two effects are mediated independently. In this study, we investigated the degree of tetanic fade that is produced in the human adductor pollicis muscle using two different techniques of drug administration—systemic i.v. injection and isolated forearm block.

METHODS AND RESULTS

After obtaining approval by the Hospital Research Ethics Committee, we studied 15 consenting patients (ASA grade I or II), allocated randomly to one of two groups: group 1 = systemic vecuronium 0.05 mg kg^{-1}; group 2 = isolated forearm vecuronium 0.3 mg. The dose of vecuronium used in each group was selected to produce 100% twitch block and have a comparable duration of action to allow assessment of fade during recovery.

Patients with medical conditions or receiving drugs known to affect neuromuscular function were excluded. All patients received i.m. pethidine 1 mg kg^{-1} with promethazine 25 mg 1 h before operation. Anaesthesia was induced with i.v. propofol 2–3 mg kg^{-1} and maintained with propofol infused at 6–10 mg kg^{-1} h^{-1} and 60% nitrous oxide in oxygen. After administration of systemic vecuronium to patients in group 1, the trachea was intubated and the lungs ventilated to maintain end-tidal carbon dioxide tension in the range 4.5–5.5 kPa. Patients in group 2 breathed spontaneously via a nasopharyngeal airway.

The ulnar nerve at the right wrist (group 1) or both wrists (group 2) was stimulated supramaximally (0.2 Hz, 0.2 ms duration) via adhesive electrodes. The mechanical evoked response of the adductor pollicis muscle was measured using a modified 20-kg load cell taped to the hand with a preload of 200–300 g, and recorded on a paper chart recorder. After 10 min, a control tetanus (50 Hz for 5 s) was administered. Ten minutes later, in group 1, vecuronium 0.05 mg kg^{-1} was administered i.v. into the contralateral arm; in group 2, a pneumatic tourniquet was inflated to greater than arterial pressure on the patient's right forearm and vecuronium 0.3 mg diluted in 20 ml of saline was injected into a vein on the dorsum of this hand. In both groups, 100% twitch depression was produced in all cases. In group 2 the arterial tourniquet was deflated after 3 min. Neuromuscular block in both groups was allowed to recover spontaneously. At 25, 50, 75 and 100% of control twitch height, a tetanic stimulus (50 Hz for 5 s) was administered to each monitored hand in both groups. During tetanic stimulation, the gain and speed of the chart recorder were adjusted to enable recordings of the response to be made.

The ratio between the tension at the end of the 5-s tetanus to the maximum tension developed initially (tetanic fade ratio (TFR)) was calculated for each tetanus. The time to 25% recovery of twitch height (T_{0-25}) and the 25–75% recovery index (RI) also were

---

N. T. A. CAMPKIN, M.B., CH.B., F.R.C.ANAES.; J. R. HOOD, M.B., CH.B., F.R.C.ANAES.; S. A. FELDMAN, M.B., B.S., F.R.C.ANAES.; Magill Department of Anaesthetics, Westminster Hospital, London SW1P 2AP. Accepted for Publication: December 15, 1992.

Correspondence to N. T. A. C.

TABLE I. *Mean (SEM) patient data,* T_{0-25}, *RI and tetanic fade ratio (TFR) at control and between 25 and 100% recovery of control twitch height.* *$P < 0.05$; **$P < 0.01$ *compared with group 1 (unpaired Student's* t *test)*

	Group 1	Group 2
n	9	6
Age (yr)	48 (34–55)	50 (35–62)
Weight (kg)	65 (4.5)	64 (4.3)
T_{0-25}	20.2 (1.2)	17.8 (2.3)
RI	9.7 (1.9)	7.4 (1.0)*
TFR		
Control	0.93 (0.01)	0.94 (0.01)
25%	0.27 (0.07)	0.78 (0.03)**
50%	0.35 (0.08)	0.86 (0.03)**
75%	0.52 (0.09)	0.89 (0.02)**
100%	0.80 (0.07)	0.92 (0.01)

measured for each patient. The TFR at each level of twitch recovery (T_{0-25} and RI) in the two groups were compared by unpaired Student's *t* test.

The groups were comparable in age and weight (table I). There was no significant difference between groups in T_{0-25}, indicating that the doses chosen were approximately equi-effective in terms of twitch depression. RI was significantly smaller in the isolated arm group ($P < 0.05$, unpaired Student's *t* test). There was no significant difference between the control TFR in each group. There was no depression of twitch response or tetanic fade produced in the contralateral hand of patients in group 2 after tourniquet release. At 25, 50 and 75% twitch recovery, there was significantly less tetanic fade in the isolated forearm of group 2 patients than after the systemic dose ($P < 0.01$).

COMMENT

In this study the same drug, administered in two different ways, produced differing degrees of tetanic fade relative to twitch depression, suggesting that the two effects are mediated independently. This finding supports that of Bowman and Webb [4], who observed that fade of the tetanic response to stimulation at 50 Hz in the cat soleus muscle was much less marked after block was produced by a small dose of tubocurarine administered i.a. than after similar twitch depression produced by a larger i.v. dose. Bowman [1] interpreted their findings as evidence that twitch depression and fade are consequences of separate actions of a competitive neuromuscular blocker; he postulated that less fade might be produced after arterial injection because there was less time for binding to "fade sites" to occur, as the drug was washed rapidly through the muscle and diluted in the general circulation. He also proposed [1] that a slower rate of binding to the fade sites would explain the different time course of twitch depression and fade observed clinically [5]. This explanation has been questioned, however [2, 3], by workers who have challenged the dual receptor hypothesis and consider that the different time course of fade and twitch depression may be a pharmacokinetic artefact. A slow rate of binding to fade sites would, however, explain the relatively little fade seen in the isolated forearm. In this technique, drug is concentrated in the muscle for 3 min before tourniquet release. This produces rapid onset of twitch depression, but may be inadequate time for binding to fade sites to occur.

After tourniquet release in the isolated forearm, the small dose of neuromuscular blocker is distributed to the general circulation. This produces no measurable effect in the contralateral arm, implying that the plasma concentration of drug is small during recovery. However, despite the small plasma concentration, depression of twitch height persists in the isolated forearm for a significant duration. In the present study, mean time for recovery to 75% twitch height was 25.2 min in the isolated forearm group, compared with 29.9 min in the systemic group. This slow recovery of twitch height in the isolated forearm is presumed to be caused by drug persisting in the biophase after tourniquet release, despite the small plasma concentration. In the absence of significant circulating drug, however, it appears that fade sites are not readily blocked by drug sustaining continued twitch depression by its persistence in the biophase. This again suggests that the sites for these two effects are distinct and may be subject to local factors affecting the ease of access and binding to each.

ACKNOWLEDGEMENT

Financial support was received from Charing Cross and Westminster Hospitals Trustees.

REFERENCES

1. Bowman WC. Prejunctional and postjunctional cholinoceptors at the neuromuscular junction. *Anesthesia and Analgesia* 1980; **59**: 935–943.
2. Bartkowski RR, Epstein RH. Relationship between train-of-four ratio and first-twitch depression during neuromuscular blockade: a pharmacokinetic/dynamic explanation. *Journal of Pharmacokinetics and Biopharmaceutics* 1990; **18**: 335–346.
3. Storella RJ, Slomowitz SA, Rosenberg H. Relationships between block-of-twitch and train-of-four fade in the mouse phrenic nerve–diaphragm preparation. *Canadian Journal of Anaesthesia* 1991; **38**: 401–407.
4. Bowman WC, Webb SN. Tetanic fade during partial transmission failure produced by non-depolarizing neuromuscular blocking drugs in the cat. *Clinical and Experimental Pharmacology and Physiology* 1976; **3**: 545–555.
5. Pearce AC, Casson WR, Jones RM. Factors affecting train-of-four fade. *British Journal of Anaesthesia* 1985; **57**: 602–606.

British Journal of Anaesthesia 1993; **70**: 583–586

CASE REPORTS

ADULT RESPIRATORY DISTRESS SYNDROME AFTER ATTEMPTED STRANGULATION

P. G. MURPHY, R. JACKSON, R. KIROLLOS, J. S. GIBSON
AND P. CHENNELLS

SUMMARY

We describe a case of severe acute lung injury after attempted strangulation. The patient presented initially with cerebral irritability and florid, non-cardiogenic pulmonary oedema which were followed by a prolonged period of the adult respiratory distress syndrome, severe sepsis and multiple system organ failure, although the patient eventually survived. The pulmonary injury following strangulation is proposed to be a result of the generation of marked subatmospheric pressures within the lungs during vigorous inspiration against an obstructed airway, although the processes involved in the so-called neurogenic pulmonary oedema are difficult to exclude. (Br. J. Anaesth. 1993; **70**: 583–586)

KEY WORDS

Lung: adult respiratory distress syndrome.

Many factors, chemical, physical and biological, have been associated with the evolution of the adult respiratory distress syndrome (ARDS) [1, 2]. The expanded definition of ARDS [3] requires exposure to a process or pathology *recognized* to be associated with the condition. Mechanical asphyxiation has not been specifically identified as a cause of ARDS. In this report, we describe the evolution of ARDS and multiple organ failure in a patient asphyxiated by manual strangulation.

CASE REPORT

A 30-yr-old Caucasian female was admitted to our Accident and Emergency Department after an anonymous telephone call to the emergency services. She was restless, opisthotonic and unresponsive; the admission Glasgow Coma Scale (GCS) score was 7 ($E_4V_2M_1$). She was normotensive (systolic/diastolic pressure 120/90 mm Hg), tachycardic (heart rate 150 beat min^{-1}) and reasonably well oxygenated, breathing oxygen-enriched air via a simple face mask (Sp_{O_2} 95%, Pa_{O_2} 13.0 kPa). She was tachypnoeic, however, with a marked stridor and fine inspiratory râles in both lung bases. Ecchymoses and petechial haemorrhages were noted on the neck, cheeks, forehead and sclera, the soft palate was congested and bilateral papilloedema noted. Fresh bruising and linear scratches, but no ligature marks, were seen on the neck. A diagnosis of attempted manual strangulation was made, and in view of the evident significant diffuse cerebral insult and the possibility of upper airway injury, the trachea was intubated and the lungs ventilated. After a rapid sequence induction using fentanyl 250 µg, etomidate 20 mg and suxamethonium 100 mg, the trachea was intubated easily with an 8.0-mm cuffed tracheal tube, although haemorrhagic supraglottic oedema was noted. Profuse, blood-stained pulmonary oedema was observed soon after intubation, and the patient was transferred to our Intensive Care Unit for further management. The subsequent clinical events have been divided into three epochs, and described semi-quantitatively using the APACHE II [4] and acute lung injury scoring [3] systems (fig. 1).

Days 1–3. The prominent features of this initial period were acute respiratory failure and cardiovascular instability. Florid pulmonary oedema was associated with diffuse patchy opacification and bilateral pneumothoraces visible on the chest x-ray (fig. 2A). Satisfactory oxygenation was only achieved by positive pressure ventilation with inspired oxygen fractions of up to 0.8, and positive end-expiratory pressure of 5–10 cm H_2O. More refractory to treatment was the systemic hypotension, which failed to respond to inotropic agents (dobutamine 20 µg kg^{-1} min^{-1}) and which improved only after infusion of 2500 ml of colloid. The site for such apparent volume loss was not clear: there were no long bone or pelvic fractures, abdominal lavage was negative and an ultrasound failed to demonstrate any hepatic, renal or splenic injury, although significant and unexpected ascites was demonstrated (fig. 2B). The considerable pulmonary oedema (which, together with the ascites, appeared responsible for the initial hypovolaemia) was persistently associated with a pulmonary artery wedge pressure less than 15 mm Hg, suggesting that it was non-cardiogenic in origin.

P. G. MURPHY, B.A., M.B., CH.B., F.R.C.ANAES., R. JACKSON, M.B., CH.B., J. S. GIBSON, M.A., M.B., B.CHIR., F.R.C.ANAES. (Department of Anaesthesia); R. KIROLLOS, F.R.C.S. (Department of Neurosurgery); P. CHENNELLS, M.B., B.S., D.M.R.D., F.R.C.R. (Department of Diagnostic Radiology); The General Infirmary at Leeds, Great George Street, Leeds LS1 3EX. Accepted for Publication: November 12, 1992.

Correspondence to P.G.M.

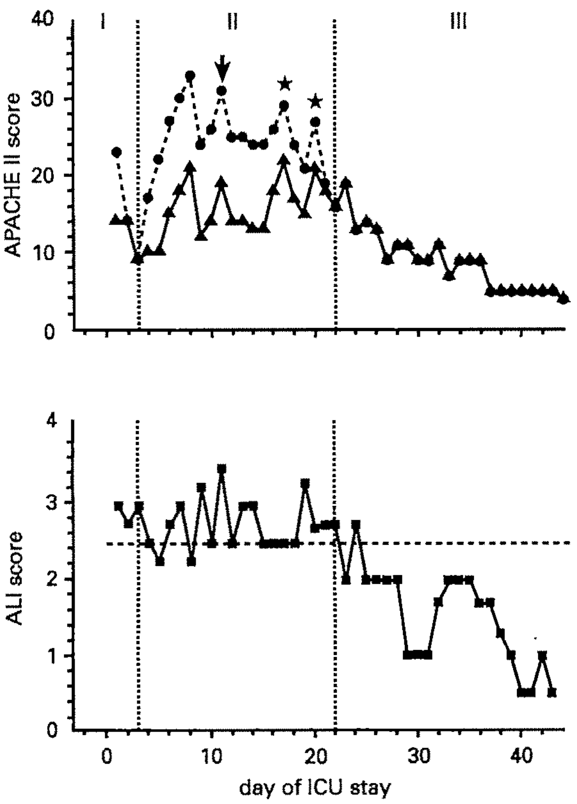


FIG. 1. APACHE II and acute lung injury (ALI) scores. The clinical course has been divided into three epochs: 1 = acute lung injury; II = ARDS and multiple organ failure; III = recovery (see text for details). APACHE II data are presented with (●) and without (▲) the contribution of the Glasgow Coma Scale score. Severe pulmonary injury is defined as an ALI score > 2.5. The deterioration in lung function on days 32–38 reflected a second period of pulmonary oedema, on this occasion as a result of fluid overload. ↓ = Administration of methylprednisolone and Centoxin; *coagulase-negative staphylococcal septicaemia.

Although the patient was awake and orientated the day after the assault, gas exchange was still sufficiently impaired to prevent weaning from artificial ventilation (the acute lung injury (ALI) score remaining greater than 2.5—the score at which lung injury is said to be severe [3]).

Days 4–22. In this second phase, persisting severe lung injury (ALI score > 2.5) was associated with non-pulmonary organ failure. Repeated episodes of severe sepsis suggestive of Gram negative septicaemia (pyrexia > 38.5 °C, cardiac index 5–6 litre min^{-1} m^{-2}, systemic vascular resistance index 450–700 dyn s m^2 cm^{-5}) were observed, but always without any microbiological identification of the responsible organism. Despite minimal sedation, conscious level deteriorated, so that the APACHE II scores, including a GCS component, were particularly increased. Persistent ileus prevented successful enteral nutrition; total parenteral nutrition was therefore required. A striking thrombocytopenia developed ($< 50 \times 10^{12}$ $litre^{-1}$), with increased concentrations of bilirubin (> 100 μmol $litre^{-1}$) and aspartate aminotransferase (70–272 iu $litre^{-1}$ (normal range 10–40 iu $litre^{-1}$)), and increased prothrombin ratio (1.4–1.9, days 2–12) suggesting modest liver disturbance. Renal function remained satisfactory throughout.

By day 11, the ALI score reached its peak value of 3.5. Bilateral pulmonary air leaks persisted with conventional positive pressure ventilation, but satisfactory oxygenation could not be maintained using high frequency jet ventilation. Core temperature (measured with the pulmonary artery flotation catheter) reached 41.6 °C and again a severe septicaemic-like haemodynamic profile was noted without any further evidence of Gram negative infection. In view of the severity of the patient's condition, it was felt necessary to treat several possibilities empirically. Thus the patient received methylprednisolone 2 g, a combination of broad spectrum antibiotics together with Centoxin 100 mg (monoclonal antibody to bacterial lipopolysaccharide, Centocor). As shown by the trend in the APACHE II scores,

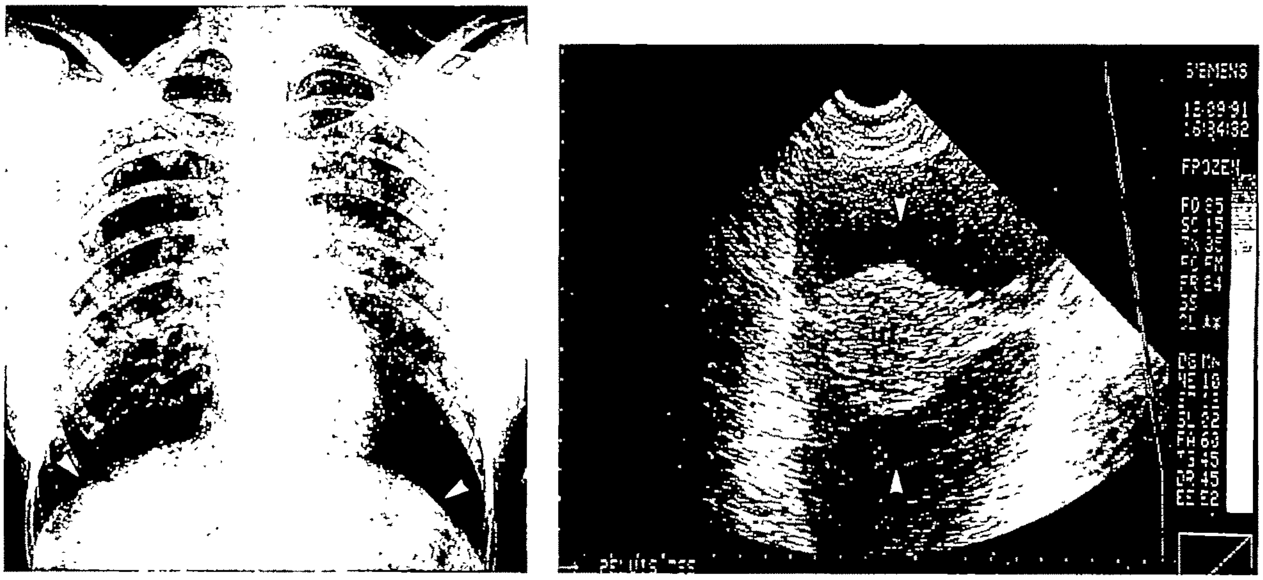


FIG. 2. Supine antero-posterior chest x-ray (left) and transverse section pelvic ultrasound (right) performed on the day of admission. The chest x-ray demonstrates florid pulmonary oedema and bilateral pneumothoraces (arrowed). The pelvic ultrasound scan shows the uterus (ut) floating in a significant quantity of ascites (arrowed).

from this point onwards the general trend was one of improvement, twice interrupted by episodes of coagulase-negative staphylococcal septicaemia (asterisks in figure 1) successfully treated with vancomycin. Conscious level improved also, as shown by the convergence of the APACHE II scores with and without the GCS score. High frequency jet ventilation was introduced successfully on day 17, and allowed the bronchopleural fistulae to heal.

Days 22–44. This third period was one of recovery. The patient was fully orientated and without any focal neurological defect. Enteral feeding was introduced successfully and the patient gradually weaned from artificial ventilation (although a continued susceptibility of the lungs to fluid overload was responsible for the deterioration in ALI score in days 31–35). The patient was transferred to a rehabilitation ward 44 days after admission to our Intensive Care Unit, and was discharged home after a total of 127 days in hospital.

DISCUSSION

The forensic features of fatal manual strangulation depend principally upon whether death occurs rapidly from vagally mediated cardiac arrest (as a result of intense carotid body/sinus stimulation), or more slowly from the combined effects of hypoxia (caused by upper airway obstruction) and intracranial hypertension (which develops when the venous drainage, but not the arterial supply, of the head is obstructed) [5]. The patient described in this case report displayed many of the features of the so-called *hypoxic* form of manual strangulation. The bruises and linear scratch marks around the neck relate to the assailant's attack itself, whilst the various manifestations of venous congestion in the head and neck (including supraglottic oedema and papilloedema) suggested significant jugular venous hypertension. It is not clear, however, if the acute brain injury seen at presentation could be explained by venous hypertension alone, or if cerebral hypoxia or ischaemia contributed.

The pulmonary consequences of fatal mechanical asphyxiation include acute focal emphysema and florid haemorrhagic pulmonary oedema. These features suggest an increase in the permeability of the alveolar–capillary barrier, and have been used to identify the cause of death in a series of homicides in which there was no external evidence of asphyxiation [6]. The florid pulmonary oedema with which this patient presented was associated with a normal pulmonary artery wedge pressure, suggesting that it was non-cardiogenic in origin. Some workers have proposed that the disruption of the alveolar–capillary barrier after asphyxiation is a consequence of the marked subatmospheric pressures developed within the lungs during forced inspiration against an obstructed upper airway [5, 6]. In this regard, this form of lung injury is similar to the well described phenomenon of pulmonary oedema after relief of upper airway obstruction associated with anaesthesia, laryngospasm, tumours, foreign bodies and goitre [7]. Other workers have shown that (experimental ligature) strangulation is associated with an intense, neurohumorally-mediated vasoconstriction which they propose may damage the pulmonary, renal and splanchnic microcirculations [8–10]. Intense pulmonary hypertension is also a frequent feature of neurogenic pulmonary oedema, although in this condition an increase in the permeability of the pulmonary microcirculation is thought to be a more fundamental pathophysiological feature, with increased pulmonary capillary pressure serving only to exacerbate alveolar flooding [11]. Either (or both) mechanisms could explain the florid pulmonary oedema seen in the early stages of this case, although the significant ascites with which this was associated suggests a process not restricted to the pulmonary microcirculation alone.

The progression to a protracted period of severe sepsis and multiple organ failure, (dominated by severe ARDS but accompanied by brain failure, persistent ileus, hepatic and bone marrow dysfunction), was unexpected and not described in a previous case report of pulmonary oedema after attempted strangulation [12]. It is tempting to attribute this to the release of toxins and microorganisms into the systemic circulation from a "leaky" gastrointestinal tract. Experimental ligature strangulation is known to disrupt the splanchnic circulation [10], and the marked ascites seen in this patient points to a similar disruption. In addition, sustained improvement was *associated* with the administration of methylprednisolone and a monoclonal antibody to bacterial lipopolysaccharide, both of which might interfere with various stages of the inflammatory pathways of severe sepsis [13].

The expanded definition of ARDS views acute lung injury as part of a spectrum of multiple system organ failure [3]. It requires that, in addition to identification of severe lung injury, there should also be evidence of non-pulmonary organ failure, with a history of clinical disorder or insult recognized to be associated with the evolution of the condition. It is not clear if, given these criteria, the term *ARDS* could be applied to the patient's initial condition, although there is no doubt that the lung injury was severe. In contrast, the later stage of established severe lung injury and multiple system organ failure clearly qualified as ARDS, although strangulation is not a recognized cause. We propose that strangulation (and possibly other forms of mechanical asphyxiation) should be considered as physical insults capable of causing severe acute lung injury and ARDS.

REFERENCES

1. Murphy PG, Jones JG. The quantitative evaluation of acute lung injury. *British Journal of Intensive Care* 1991; 1: 110–117.
2. Wiener-Kronish JP, Gropper MA, Matthay MA. The Adult Respiratory Distress Syndrome: definition and prognosis, pathogenesis and treatment. *British Journal of Anaesthesia* 1990; 65: 107–129.
3. Murray JF, Matthay MA, Luce J, Flick MR. An expanded definition of the adult respiratory distress syndrome. *American Review of Respiratory Disease* 1988; 138: 720–723.
4. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: A severity of disease classification. *Critical Care Medicine* 1985; 13: 818–829.

British Journal of Anaesthesia 1993; 70: 587–590

ANAESTHETIC IMPLICATIONS OF THE ANTI-CARDIOLIPIN ANTIBODY SYNDROME

G. MENON AND J. ALLT-GRAHAM

SUMMARY

The anti-cardiolipin antibody syndrome (or anti-phospholipid antibody syndrome) is characterized by the presence of autoantibodies to phospholipids. Its major association is with systemic lupus erythematosus. It is characterized further by in vitro *prolongation of phospholipid-dependent coagulation tests. However,* in vivo *it is associated with a markedly increased incidence of thrombosis, both arterial and venous. We describe the case of a 36-yr-old female patient with the anti-cardiolipin antibody syndrome who presented initially for diagnostic laparoscopy and later for exploratory laparotomy. Her postoperative course after the first general anaesthetic was complicated by disseminated intravascular coagulation and adult respiratory distress syndrome. After the second operation, she deteriorated further with worsening cardiac, renal and respiratory function and eventually died. As far as we are aware, this is the first reported case of the anti-cardiolipin antibody syndrome in anaesthetic literature. Further aspects of this puzzling condition and its anaesthetic implications are discussed.* (Br. J. Anaesth. 1993; **70**: 587–590)

KEY WORDS

Complications: anti-cardiolipin antibody syndrome.

The anti-cardiolipin antibody syndrome is characterized by the presence of anti-phospholipid antibodies in patients who show a tendency to recurrent thromboses (both arterial and venous), recurrent abortions, thrombocytopenia and neurological disease [1, 2]. The term "cardiolipin" is derived from the antigen used to test for these antibodies which utilizes a lipid component of bovine heart tissue [3]. The syndrome has been described by several authors [4, 5].

The exact role of these antibodies in the syndrome is uncertain. There is a controversy in the medical literature as to whether they are aetiological agents of pathogenesis or if they are just simple markers of a high-risk population [6]. About 50% of patients with this syndrome have systemic lupus erythematosus (SLE). Others may have other connective tissue diseases (e.g. scleroderma). The prevalence of these anti-phospholipid antibodies in patients with SLE has been estimated, at various times, as 5–55% [7, 8].

These patients may present to the anaesthetist for routine and emergency operations, and in the intensive care unit. In addition, as SLE occurs primarily in women in the childbearing age group, with a female:male ratio of approximately 10:1, there is a greater incidence in obstetric patients [9]. The anaesthetist may be involved in the care of these high risk parturients, especially as operative delivery is common. The anaesthetic literature lacks any references on this subject. We present a case report of this condition.

CASE REPORT

A 36-yr-old Indonesian female, gravida 2, para 0, presented to the gynaecologists with a 1-week history of lower abdominal pain, high grade pyrexia and a brief episode of vaginal bleeding. An ultrasound scan demonstrated a pelvic mass consistent with a necrotic ovarian tumour. SLE had been diagnosed 10 years earlier ("lupus like", rather than classical SLE). She was receiving warfarin 3 mg and aspirin 75 mg daily. There was a history of a stroke in the past, but the patient was unable to provide further details because of her and her family's inability to speak English. There were no residual signs of a stroke except for partial blindness in one eye. In addition, her old notes from another hospital were not available at the time. Investigations revealed a haemoglobin concentration of 8.0 g dl^{-1} and a greatly prolonged prothrombin time (PT) and activated partial thromboplastin time (APTT), with normal platelets. Before diagnostic laparoscopy, the warfarin was stopped and the coagulation profile corrected with fresh frozen plasma (FFP) to bring the International normalized ratio within the therapeutic range. Anaesthesia was induced with thiopentone and suxamethonium and maintained with enflurane, fentanyl and vecuronium. Laparoscopy confirmed the presence of a large ovarian fibroma or a sub-serous fibroid.

After operation in the recovery room, the patient was clinically stable, but developed significant hypoxaemia when oxygen was discontinued. Oxygen therapy was re-commenced and she was transferred back to the ward. In the ward, anticoagulation was

---

G. MENON, M.B., B.S., F.R.C.ANAES.; J. ALLT-GRAHAM, M.B., B.S., B.SC., F.F.A.R.A.C.S., F.R.C.ANAES.; Department of Anaesthetics, St George's Hospital, Blackshaw Road, Tooting, London SW17 0QT. Accepted for Publication: November 24, 1992.

recommenced with heparin infusion. The patient developed further hypoxaemic episodes in the ward over the next 1 week, accompanied by pleuritic chest pains and shortness of breath. However, ventilation–perfusion scans were not consistent with pulmonary embolism. She continued to have persistent pyrexia (> 39 °C) while receiving broad spectrum antibiotics. All investigations for the cause of the fever were inconclusive (blood cultures, viral serology, malarial parasites etc.).

At this point, the patient's old notes became available from another hospial. The records revealed a significant history of major thrombotic episodes. Aged 20 yr, the patient had developed sudden unexplained venous thrombosis of her left leg. At the age of 26 yr, after an appendicectomy, she developed retinal vein thrombosis. Investigations led to a diagnosis of SLE although she was anti-nuclear antibody negative. At the age of 32 yr, when 27 weeks pregnant, she underwent emergency Caesarean section under general anaesthesia. Three days post-partum she developed a brain-stem infarct. At this time, she was found to be strongly anti-cardiolipin antibody positive and anticoagulation was commenced with warfarin. Her next presentation was at the age of 35 yr when, after dilatation and curettage for a miscarriage, she developed a cerebellar infarct.

In the light of this history of major thrombotic events and a diagnosis of the anti-cardiolipin antibody syndrome now available, full heparinization was continued. In spite of this, the patient deteriorated further with continuing high pyrexia, becoming semi-conscious with neck stiffness and a blood picture suggestive of disseminated intravascular coagulation. CT scan of the head demonstrated old cerebellar and basal ganglia infarcts, but no new changes. The cause of her sudden neurological deterioration was unclear. High-dose steroid therapy was started and antibiotics were continued.

The patient was admitted to the intensive care unit for monitoring of her cardiovascular and neurological state. She made a rapid neurological recovery with resolution of neck stiffness and recovery of full consciousness. However, she remained tachycardic (> 150 beat min^{-1}), pyrexic (> 39 °C), tachypnoeic and hypoxaemic. Echocardiogram was normal. While receiving full heparinization, the patient developed further episodes of pleuritic chest pain. Plasmapheresis was commenced to decrease her concentration of anti-cardiolipin antibody. She continued to deteriorate, with decreasing renal and respiratory function. A pulmonary artery thermodilution catheter was inserted and revealed a central venous pressure of 9 mm Hg, pulmonary artery pressures of 30/18 mm Hg, pulmonary artery wedge pressure of 19 mm Hg, and cardiac index of 1.2. A repeat echocardiogram (within 24 h of the previous one) revealed a large, poorly functioning left ventricle with poor global systolic contraction. Treatment with inotropes and vasodilators (dopamine, dobutamine, adrenaline, nitrates) produced some improvement in cardiac index. In view of the patient's deterioration and intra-abdominal signs suggestive of a necrotic ovarian/uterine fibroid, it was decided to proceed to exploratory laparotomy.

Heparin was stopped 2 h before operation and anaesthesia induced in the operating theatre with full haemodynamic monitoring. A rapid-sequence induction was performed with etomidate and suxamethonium and anaesthesia maintained with atracurium and incremental doses of fentanyl. The intraoperative course was uneventful. The patient remained haemodynamically stable, with good gas exchange. Laparotomy confirmed the presence of a necrotic ovarian fibroid which was removed. Blood loss was estimated at 300 ml. However, in view of the continuous oozing and decreasing haemoglobin concentration, she was transfused with 1 unit of blood, 6 units of platelets and 2 units of FFP.

The patient was transferred back to the intensive care unit after operation, with full circulatory and ventilatory support. On arrival in the unit, she developed increasing facial oedema with mottled, blueish macular discolouration of the skin and congested neck veins. However, central venous pressure and lung inflation pressures were normal and an echocardiogram did not reveal any new changes. There were no signs of superior vena cava obstruction or cardiac tamponade. Blood-gas analyses revealed severe metabolic acidosis, but normal gas exchange.

Her general condition continued to deteriorate with worsening renal, cardiac and respiratory function in spite of haemodyalysis, full inotropic support and continued ventilation. She died 10 days after admission for the initial complaint.

Postmortem revealed only the presence of numerous scattered petechial haemorrhages over the myocardium with left ventricular hypertrophy. The coronary arteries were normal. The cause of death was recorded as cardiac failure. There was pulmonary oedema in the lungs, but no evidence of infarct or emboli. Apart from old infarcts in the basal ganglia and cerebellum, the rest of the postmortem examination was unremarkable.

DISCUSSION

The unfortunate demise of this patient prompted us to search the anaesthetic literature on the anaesthetic implications of the anti-cardiolipin syndrome. We were unable to find any information on this subject, apart from one reference to the lupus anticoagulant [10]. A search of the general medical literature revealed a large number of conflicting facts, reports and ideas [1–8].

The anti-cardiolipin antibodies may be part of a family of autoantibodies. A cause and effect relation between presence of antibodies and complications has not been established. About 50% of patients with this syndrome have SLE, although the prevalence of these antibodies in SLE patients may vary from 5 to 55% [7, 8].

Patients with this syndrome who have SLE are usually "lupus like" [11]. The revised American Rheumatism Association criteria for diagnosis of classical SLE requires the presence of four or more typical symptoms (e.g. malar rash, arthritis, photo-sensitivity, renal involvement) [12]. Most of the patients with classical SLE (> 90 %) are antinuclear antibody (ANA) positive. Patients who have fewer than four of the above criteria are labelled "lupus-like" and are usually ANA negative (similar to our patient).

The diagnosis of this syndrome is confirmed by specific tests:

(a) The presence of these antibodies blocks the activity of the X_a–V_a–Ca^{2+} phospholipid complex required to convert prothombin to thrombin. *In vitro*, the phospholipid-dependent coagulation tests (APTT and kaolin cephalin clotting time (KCCT)) are prolonged, although prothrombin time (PT) and thrombin clotting time are usually normal.

(b) The most sensitive and specific test for the presence of the anti-cardiolipin antibodies is an enzyme-linked immunosorbent assay (ELISA) [13]. The combination of these two tests gives the greatest degree of sensitivity and specificity.

In vivo, these patients have a markedly increased incidence of thromboses. There are many theories on the aetiology of thromboses, but so far none has been substantiated. Current knowledge suggests that these antibodies mediate thrombosis by acting at several sites of action. When platelets are pre-activated by a variety of stimuli, they expose the negatively-charged phospholipids on their surface to the antibodies, resulting in platelet aggregation.

The antibodies also react with surface phospholipids in endothelial cells, inhibiting the production of prostacyclin and interfering with the action of thrombomodulin and protein C in endothelial cells. Thus platelet aggregation is promoted. The clinical manifestations of platelet aggregation and thrombosis could lead to thrombocytopenia [8].

In 40–50 % of patients with this syndrome, there is a history of *thromboses*, both arterial and venous, often recurrent, at unusual sites and occurring spontaneously. This picture was typical of our patient. The venous system involved may be at unusual sites such as the renal, retinal and adrenal venous systems. In addition, one case of superior vena caval occlusion in anti-cardiolipin antibody syndrome has been described [14]. Our patient developed a similar picture after operation, with increasing facial oedema and congested neck veins. Venography to confirm thrombosis is not recommended in these patients.

The obstetric history may show recurrent spontaneous *abortions*. Presence of circulating anti-cardiolipin antibodies is associated with increased fetal loss in all trimesters and approaches 80 % in patients with high titres of antibodies. This was again typical of our patient. The presence of the anti-cardiolipin syndrome in patients with SLE makes the pregnancy a high-risk one. There is an increased incidence of pre-eclamptic toxaemia in patients with this syndrome [15].

A prospective study looked at the incidence of cardiac complications in patients with SLE with and without the anti-cardiolipin antibody syndrome [16]. There was a 54 % incidence of cardiac complications in the SLE group. However, in the presence of SLE and the anti-cardiolipin syndrome, the incidence was close to 80 %. The myocardial changes seen in our patient were those characterized in this study—global and left ventricular dysfunction.

Neurological complications in the anti-cardiolipin antibody syndrome comprise transient ischaemic attacks, strokes and neuropsychiatric disturbances [17]. Our patient showed such a picture, with a sudden neurological deterioration followed by recovery.

In addition, there is another presentation described recently [18], with acute, widespread, non-inflammatory vascular occlusions resulting in major organ dysfunction. The trigger factor seems to be infection, changing the anticoagulation regimen, or both [19]. Patients with this syndrome have a tendency to develop thromboses even while receiving full anticoagulation. Our patient had classical signs suggestive of multiple pulmonary emboli even while receiving full heparinization.

Patients with SLE present a significant morbidity and mortality. The 5-yr survival rate is approximately 75 %. The morbidity and mortality is increased substantially in the presence of the anti-cardiolipin antibody syndrome, although no figures are available as yet.

We recommend the following management regimen in patients with the anti-cardiolipin antibody syndrome:

All patients with SLE and a history of recurrent abortions, thrombotic episodes, or both, should be screened for the antibody. If positive, and in the presence of high titres, the complications are increased substantially.

In patients with SLE and in the presence of anti-cardiolipin antibodies but with no history of thrombosis and a normal coagulation screen (except for prolonged APTT), appropriate s.c. preoperative doses of unfractionated heparin or low molecular weight heparin are recommended.

Patients with a history of one or more thrombotic events require permanent anticoagulation and there should be close liaison with haematologists for this purpose. It is important to maintain these patients in their anticoagulated state, with warfarin or aspirin. In the perioperative period, carefully controlled heparin therapy by infusion or given s.c. is recommended.

Regional anaesthesia is generally contraindicated in patients receiving high-dose warfarin. The use of regional techniques in those receiving low-dose aspirin, even with a normal bleeding time, is debatable. The safety of regional blocks in a patient who has the anti-cardiolipin antibody syndrome and prolonged APTT is unknown. The use of regional techniques in the uncomplicated syndrome is probably not associated with any complications. Regional techniques would naturally be contraindicated in the presence of an overt coagulopathy, decreased platelet concentrations, or both.

Patients who have the diffuse coagulopathy, vasculopathy picture (of our patient) need intensive haemodynamic monitoring in the intensive care unit with plasmapheresis (to decrease the titre of the anti-cardiolipin antibody), high-dose steroids, full heparinization and, if disseminated intravascular coagulation is present, appropriate replacement. In the presence of a circulating anticoagulant, the adequacy of heparinization is monitored preferably with a heparin assay.

From this case history and available literature, the following anaesthetic recommendations would seem appropriate:

(a) All prophylactic measures should be taken to prevent thromboses. Use of anti-embolic stockings, avoiding dehydration and maintaining normothermia should be mandatory.

(b) Drugs likely to precipitate or exacerbate the condition (e.g. hydralazine) should be avoided.

(c) Infection, which is another trigger source for lupus and for initiating coagulopathy, should be prevented by routine antibiotic therapy.

(d) Blood transfusion should be avoided if possible, as this has also been implicated as a trigger factor.

(e) Standard monitoring (heart rate, oximetry, capnograph, ECG, etc.) may be all that is needed for routine cases. In addition, patients may need CVP/pulmonary artery monitoring in the presence of severe cardiac, renal or pulmonary artery involvement.

(f) Postoperative hypoxaemia, when it occurs, may be indicative of ARDS or pulmonary thromboembolism and needs investigation and monitoring in an intensive care unit. If signs of acute widespread coagulopathy occur, early aggressive plasmapheresis with high-dose steroids and immunosuppression may be indicated.

ACKNOWLEDGEMENT

We thank Dr Parker-Williams, Consultant Haematologist, St George's Hospital for his advice.

REFERENCES

1. Harris EN. Antiphospholipid and antibodies. *British Journal of Haematology* 1990; 74: 1–9.
2. Triplett DA, Brandt JT. Lupus anticoagulants: misnomer, paradox, riddle, epiphenomenon. *Haematology and Pathology* 1988; 2: 121–143.
3. Pangborn MC. A new serologically active phospholipid from beef heart. *Proceedings of the Society Experimental Biological Medicine* 1941; **48**: 484–486.
4. Asherson RA. A primary anti-phospholipid syndrome. *Journal of Rheumatology* 1988; **15**: 1742–1746.
5. Hughes GRV, Harris EN, Ghavari AE. The anti-cardiolipin syndrome. *Journal of Rheumatology* 1987; **13**: 486–489.
6. Triplett DA, Brandt JT, Musgrave KA, Orr CA. The relationship between lupus anticoagulants and antibodies to phospholipid. *Journal of the American Medical Association* 1988; **259**: 550–554.
7. Alarcon-Segovia D, Deleze M, Oria CV. Anti-phospholipid antibodies in SLE. A prospective analysis of 500 consecutive patients. *Medicine* 1989; **68**: 353–365.
8. Cameron JS, Frampton G. The "anti-phospholipid syndrome" and the "lupus anticoagulant". *Paediatric Nephrology* 1990; 4: 663–678.
9. Hayslett JP, Reece EA. SLE in pregnancy. *Clinics in Pharmacology* 1985; **12**: 539.
10. Malinow AM, Rickford WJK, Mokriski BLK, Saller DN, McGuinn WJ. Lupus anticoagulant—implications for obstetric anaesthetists. *Anaesthesia* 1987; **42**: 1291–1293.
11. Hughes GRV, Asherson RA. Atypical lupus with special reference to ANA-negative lupus and lupus subsets. In: Grunfeld JP, Maxwell MH, eds. *Advances in Nephrology.* Chicago: Year Book Medical Publishers, 1985; 333–345.
12. Tan EM, Cohen AS, Fries JF. The 1982 revised criteria for the classification of SLE. *Arthritis and Rheumatology* 1982; **25**: 1271–1277.
13. Loizou S, McCrea JD, Rudge AC, Reynolds R, Boyle CC, Harris EN. Measurement of anticardiolipin antibodies by an enzyme-linked immunosorbent assay (ELISA): standardization and quantitation of results. *Clinical and Experimental Immunology* 1985; **62**: 738–745.
14. Tomer Y, Kessler A, Eyal A, Many A, Shoenfeld Y. Superior vena cava occlusion in a patient with anti phospholipid antibody syndrome. *Journal of Rheumatology* 1991; **18**: 95–97.
15. Taylor PV, Skerrow SM. Pre-eclampsia and anti-phospholipid antibody. *British Journal of Obstetrics and Gynaecology* 1991; **98**: 604–606.
16. Nihoyannopoulos P, Gomez PM, Joshi J, Loizou S, Walport MJ, Oakley CM. Cardiac abnormalities in Systemic Lupus Erythematosus—association with raised anticardiolipin antibodies. *Circulation* 1990; **82**: 369–375.
17. Levine SR, Welsh KMA. The spectrum of neurologic disease associated with anti-phospholipid antibodies. *Archives of Neurology* 1987; **44**: 876–883.
18. Greisman SG, Thayaparan RS, Godwin TA, Lockshin MD. Occlusive vasculopathy in Systemic Lupus Erythematosus—association with anticardiolipin antibody. *Archives of Internal Medicine* 1991; **151**: 389–391.
19. Asherson RA, Chan JKH, Harris EN, Gharavi AE, Hughes GRV. Anticardiolipin antibody, recurrent thrombosis and warfarin withdrawal. *Annals of Rheumatic Diseases* 1985; **44**: 823–825.

British Journal of Anaesthesia 1993; 70: 591–592

SPONTANEOUS REPOSITION OF A DISLOCATED ARYTENOID CARTILAGE

A. GAUSS, H. S. TREIBER, J. HAEHNEL AND H. S. JOHANNSEN

SUMMARY

We report a patient suffering from arytenoid cartilage dislocation after difficult tracheal intubation and the abrupt spontaneous reposition in the course of severe vomiting 1 month after the operation. Predisposing factors for the unusual reposition are discussed. (Br. J. Anaesth. 1993; **70**: 591–592)

KEY WORDS

Complications: arytenoid dislocation. Intubation, tracheal.

Arytenoid dislocation is a rare event and complication of tracheal intubation [1–11]. It may cause the following changes: alteration in vocal quality (weak voice, whisper, hoarseness, aphonia) [3, 5, 8–10], diminished airway (stridor) [2, 6, 8, 11], sore throat, or painful swelling [1].

Laryngoscopy reveals an immobile vocal cord. Correct diagnosis is essential, to exclude neurogenic vocal cord paralysis, as the management of the two conditions is different. Early reposition of the dislocated arytenoid is required when dislocation has occurred.

CASE REPORT

A 60-yr-old man was scheduled for radical prostatectomy and was classified ASA II. He reported a chronic dry cough for several years, but an ENT examination 6 months earlier had not revealed any pathology except what was described as a hypersensitive bronchial system. In the past, he had undergone three general anaesthetics, one with intubation 21 yr previously. Difficulty with intubation was not expected, as the Mallampati classification was I [12], with mouth opening 5 cm.

Anaesthesia was induced and laryngoscopy, performed with a No. 3 MacIntosh blade, was difficult. It was classified as Cormack grade 3 [13] (epiglottis only visible), and accomplished by an experienced senior registrar at the first attempt with a 8.5-mm i.d. super-safety-tube (34 CH, Ruesch, Germany) using a stylet. The tip of the tube was easily pushed down around the stylet lying in the trachea and rotation of the tube was not required. With the exception of a bradycardia of 40 beat min^{-1} after administration of suxamethonium and during intubation, there was no other anaesthetic or operative problem. A nasogastric tube (14-gauge) was passed without difficulty at the time of intubation. Because of hypothermia at the end of surgery, mechanical ventilation was continued for 8 h after operation. At 12 h after tracheal intubation, the trachea was extubated without difficulties, with the tube cuff deflated.

On the first day after operation the patient complained of feeling a bolus in the throat. ENT examination on the same day revealed distinct oedema of the soft palate on both sides, with unremarkable larynx and vocal cords.

Follow-up examination by another otorhinolaryngologist showed "a discreet oval-shaped insufficiency of the closure of both vocal cords," but no signs of trauma caused by tracheal intubation. The continuing aphonia of the patient was suspected to be caused partially by his chronic obstructive bronchitis.

A third ENT consultation described paresis of the right vocal cord with normal mobility of both cricoarytenoid junctions, no haematoma and no inflammation.

Three weeks later, examination under local anaesthesia and review of the recent videoendoscopy revealed dislocation of the left arytenoid cartilage.

The previous differences in diagnosis were explained by the difficulties in laryngoscopy in this patient and his tendency to choke on examination.

Reposition of the cartilage under general anaesthesia was planned for the 26th day. Laryngoscopy revealed Cormack grade 3, confirmed by a second registrar, but repositioning could not be performed because of reduced mobility of the patient's head. Repositioning under local anaesthesia was scheduled subsequently, but not carried out because in the meantime, the patient was admitted to a different hospital with symptoms of pancreatitis and biliary colic. At that time aphonia persisted, but after a severe bout of vomiting, his voice changed abruptly to normal.

Final examination under indirect microlaryngoscopy revealed no dislocation of the arytenoid cartilage. The patient was content and did not notice any difference in his voice compared with time before the incident. Stroboscopy of the vocal cords was normal.

ALBRECHT GAUSS, M.D., HANS S. TREIBER, M.D., JONAS HAEHNEL, M.D. (Department of Anaesthesiology); HELGE S. JOHANNSEN, M.D (Department of Otolaryngology); University of Ulm, Prittwitzstr. 43, 7900 Ulm, Germany. Accepted for Publication: November 30, 1992.

DISCUSSION

In our patient, tracheal intubation, using a stylet, was difficult and the vocal cords and arytenoid cartilages were not seen. Insertion of the nasogastric tube and tracheal extubation were performed without difficulty and tracheal extubation occurred 8 h after operation (short-term intubation). Consequently, we believed that the persisting aphonia was a direct result of tracheal intubation and, after several laryngological examinations, the cause of the aphonia was found to be dislocation of the left arytenoid cartilage.

Review of the literature indicates that, the left side is involved in the majority of cases of arytenoid dislocation [1, 3, 5–10]. We agree with Quick and Merwin [1] that the left arytenoid is at greater risk of the injury.

There are several possible causes of dislocation of the arytenoid. In our patient, the most likely explanations are either dislocation by pressure from the tip of the tube or the stylet [2] or trapping of the arytenoid between the stylet and the tube. A further explanation suggested by Quick and Merwin [1], although less likely in our patient, is the force exerted by the convex curvature of the distal third of the tracheal tube on the arytenoid cartilage.

To avoid trauma to the arytenoids, it might have been helpful to rotate the tube 90° anticlockwise before it approached the larynx, as proposed by Cossham [14].

Diagnosis may have been made earlier using computed tomography [8], especially in our patient, in whom direct and indirect examination of the larynx was not easy to perform and led to several misinterpretations. Oedema or haematoma of the cricoarytenoid region may also have delayed correct diagnosis [4, 7].

Arytenoid cartilage dislocation after tracheal intubation is uncommon, probably because of the wide range of passive motion allowed by the cricoarytenoid joint [1]. Habitual dislocation [15] can be excluded in this case, as our patient experienced no such event during previous tracheal anaesthesia. It is possible that chronic bronchitis with frequent coughing may cause loosening of the cricoarytenoid joint ligaments, thereby making possible dislocation of the arytenoid cartilage and its abrupt spontaneous reposition by comparatively minor forces [2].

The first case of spontaneous repositioning was reported by Rudert [7]. It occurred while his patient was coughing after accidentally aspirating a piece of an apple. Another case of spontaneous repositioning of bilateral dislocated arytenoids was reported by Chatterji, Gupta and Mishra [11]; restoration of the arytenoids to their normal position was associated with violent coughing. Here we present the third case of spontaneous repositioning of an arytenoid dislocation. The dislocation was caused by tracheal intubation and its spontaneous reposition occurred in the course of severe vomiting. The predisposing factor for this unusual reposition was probably chronic bronchitis.

REFERENCES

1. Quick CA, Merwin GE. Arytenoid dislocation. *Archives of Otolaryngology* 1978; **104**: 267–270.
2. Schultz-Coulon H-J. Luxation des Arytaenoidknorpels als Intubationsschaden. *HNO* 1974; **22**: 242–245.
3. Prasertwanitch Y, Schwarz JJH, Vandam LD. Arytenoid cartilage dislocation following prolonged endotracheal intubation. *Anesthesiology* 1974; **41**: 516–517.
4. Kambic V, Radsel Z. Intubation lesions of the larynx. *British Journal of Anaesthesia* 1978; **50**: 587–590.
5. Komorn RM, Smith CP, Erwin JR. Acute laryngeal injury with short-term endotracheal anesthesia. *Laryngoscope* 1973; **83**: 683–690.
6. Castella X, Gilabert J, Perez C. Arytenoid dislocation after tracheal intubation: an unusual cause of acute respiratory failure? *Anesthesiology* 1991; **74**: 613–615.
7. Rudert H. Über seltene intubationsbedingte innere Kehlkopftraumen. Rekurrensparesen, Distorsionen und Luxationen der Cricoarytaenoidgelenke. *HNO* 1984; **32**: 393–398.
8. Dudley JP, Mancuso AA, Fonkalsrud EW. Arytenoid dislocation and computed tomography. *Archives of Otolaryngology* 1984; **110**: 483–484.
9. Frink EJ, Pattison BD. Posterior arytenoid dislocation following uneventful endotracheal intubation and anesthesia. *Anesthesiology* 1989; **70**: 358–360.
10. Nicholls BJ, Packham RN. Arytenoid cartilage dislocation. *Anaesthesia and Intensive Care* 1986; **14**: 196–198.
11. Chatterji S, Gupta NR, Mishra TR. Valvular glottic obstruction following extubation. *Anaesthesia* 1984; **39**: 246–247.
12. Mallampati SR, Gatt SP, Gugino LD, Desai SP, Waraksa B, Freiberger D, Liu PL. A clinical sign to predict difficult tracheal intubation: a prospective study. *Canadian Anaesthetists' Society Journal* 1985; **32**: 429–434.
13. Cormack RS, Lehane J. Difficult tracheal intubation in obstetrics. *Anaesthesia* 1984; **39**: 1105–1111.
14. Cossham PS. Difficult intubation. *British Journal of Anaesthesia* 1985; **57**: 239.
15. Tarneaud J. La laxité des articulations du larynx. *Annales d'Oto-Laryngologie et de Chirurgie Cervico Faciale* 1949; **66**: 293–299.

British Journal of Anaesthesia 1993; **70**: 593–600

CORRESPONDENCE

"CONCORDE NOSE" IN WHITACRE SPINAL NEEDLES

Sir,—We wish to report a complication of the 25-gauge Vygon Whitacre spinal needle in two patients.

A 72-yr-old ASA II female with a fractured right neck of femur presented for insertion of Pugh nail under spinal anaesthesia. She was placed in the left lateral position and, under aseptic conditions, a 25-gauge Vygon Whitacre needle was inserted via an introducer at the L3–L4 interspace. However, the needle struck bone and was immediately withdrawn. The resulting damage to the tip of the spinal needle is demonstrated on the lower right needle in figure 1.

A 27-yr-old ASA I female was to undergo elective Caesarean section. She was placed in the left lateral position and a 25-gauge Vygon Whitacre needle was advanced slowly at the L2-3 interspace. Firm resistance was felt and the needle could not be advanced any further. The needle was removed and the tip found to be distorted as shown in figure 1 (upper left needle).

Similar bending of the tip is a potential problem with Sprotte needles. In the U.S.A., it is recommended that, if the Sprotte needle tip is bent after encountering bone, the needle should be removed and not re-used [1].

The visible distortion of the atraumatic tips may result in increased tearing of dural fibres and possible increase in incidence of postdural puncture headache. If a Whitacre needle with a bent distal tip is re-used, there is also a risk of fracture of the tip, with possible infective and neurological sequelae. We suggest that, if a Whitacre needle strikes bone, the needle should be removed and discarded and a substitute needle inserted.

G. A. McLeod
D. Carson
J. Bannister
Ninewells Hospital
Dundee

1. Havel's Incorporated. 3726 Lonsdale Avenue, Cincinatti, Ohio, 45227, U.S.A.

PERIPHERAL NERVE DAMAGE AND REGIONAL ANAESTHESIA

Sir,—The paper of Rice and McMahon elegantly illustrates the point that fine-bore needles inserted into isolated rat sciatic nerves are capable of producing significant and protracted damage [1]. There are some anecdotal clinical data to support this view [2]. As a consequence, the aim of most people who use local anaesthetic blocks is not to penetrate the nerve [3–6]. Because of the relative advantages of local anaesthetic blocks over other techniques [7], and the possibility of prolonged postoperative analgesia [8], it is important that we strive to reduce the risk of intraneural injection as opposed to abandoning local anaesthetic blocks *per se*.

The guidelines for local anaesthetic blocks need re-examination; to that end we are in agreement with the editorial by Chambers [9]. A particular issue is the suggestion that local anaesthetic blocks should not be used in anaesthetized or sedated patients. Is it not possible that most patients would respond to painful intraneural injections in the presence of light sedation/anaesthesia? In our experience, they often withdraw in response to cold antiseptic used on the skin. Therefore, should we stop using local anaesthetic techniques in sedated and anaesthetized patients in response to one poorly described case report of median nerve injury after a wrist block under general anaesthesia? There are many other instances of nerve injury unrelated to local anaesthetic techniques [10, 11].

Despite the evidence of Rice and McMahon [1], we feel that long-bevelled cutting needles should not be used. Some 75% of anaesthetics in this hospital are supplemented by local anaesthesia, and complications have occurred only in patients in whom long-bevelled needles have been used in relatively fixed nerves. Does the risk of intraneural injection still exist if: 1) nerves are not fixed within the surrounding tissue—such as the brachial plexus [12, 13], and probably the ulnar and median nerves at the elbow; 2) a nerve stimulator, short-bevelled needle and care are used? In our clinical experience using such techniques, we have never had evidence to suggest intraneural penetration in either awake or sedated patients. Is the risk worth taking of using long-bevelled needles together with paraesthesiae, when several publications have demonstrated that paraesthesia techniques are not superior to nerve stimulator techniques [3, 14], and long-bevelled needles are obviously sharper and thus more likely to penetrate the nerve?

A. P. Baranowski
R. J. Buist
Medway Hospital
Gillingham

1. Rice ASC, McMahon SB. Peripheral nerve injury caused by injection needles used in regional anaesthesia: influence of bevel configuration, studied in a rat model. *British Journal of Anaesthesia* 1992; **69**: 433–438.
2. Selander D, Edshage S, Wolf T. Paresthesia or no paresthesia? Nerve lesions after axillary plexus block. *Acta Anaesthesiologica Scandinavica* 1979; **23**: 27–33.
3. Baranowski AP, Pither CE. A comparison of three methods of axillary brachial plexus anaesthesia. *Anaesthesia* 1990; **45**: 362–365.

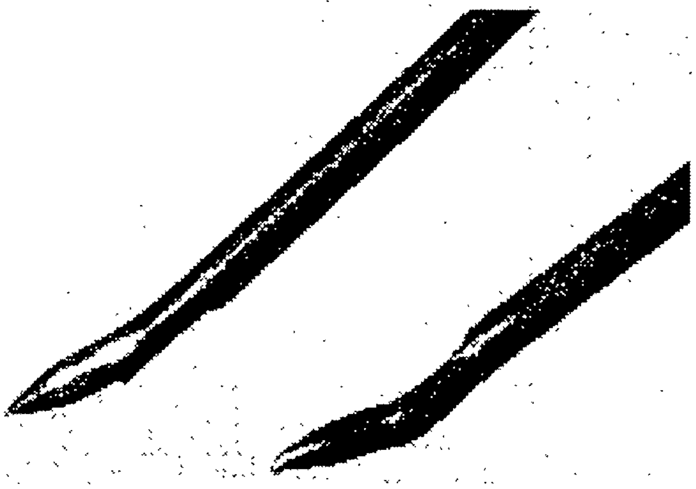


Fig. 1. Damage sustained by two 25-gauge Vygon Whitacre spinal needles during insertion to lumbar interspaces.

4. Pither CE, Raj PP, Ford DJ. The use of peripheral nerve stimulators for regional anesthesia. A review of experimental characteristics, technique and clinical applications. *Regional Anesthesia* 1985; **10**: 49–58.
5. Selander D. Catheter technique in axillary plexus block. Presentation of a new method. *Acta Anaesthesiologica Scandinavica* 1977; **21**: 324–329.
6. Ang ET, Lassale B, Goldfarb G. Continuous axillary brachial plexus block—a clinical and anatomical study. *Anesthesia and Analgesia* 1984; **63**: 680–684.
7. McQuay HJ. Pre-emptive analgesia. *British Journal of Anaesthesia* 1992; **69**: 1–3.
8. Rosenblatt R, Pepitone-Rockwell F, McKillop MJ. Continuous axillary analgesia for traumatic hand injury. *Anesthesiology* 1979; **51**: 565–566.
9. Chambers WA. Peripheral nerve damage and regional anaesthesia. *British Journal of Anaesthesia* 1992; **69**: 429–430.
10. Kroll DA, Caplan RA, Posner K, Ward RJ, Cheney FW. Nerve injury associated with anesthesia. *Anesthesiology* 1990; **73**: 202–207.
11. Britt BA, Gordon RA. Peripheral nerve injuries associated with anaesthesia. *Canadian Anaesthetic Society Journal* 1964; **11**: 514.
12. Selander D. Axillary plexus block: paresthetic or perivascular. *Anesthesiology* 1987; **66**: 726–728.
13. Partridge BL, Katz J, Benirschke K. Functional anatomy of the brachial plexus sheath: implications for anesthesia. *Anesthesiology* 1987; **66**: 743–747.
14. Goldberg ME, Gregg C, Larijani GE, Norris MC, Marr AT, Seltzer JL. A comparison of three methods of axillary approach to brachial plexus blockade for upper extremity surgery. *Anesthesiology* 1987; **66**: 814–816.

Sir,—We thank Drs Baranowski and Buist for their interest in our paper and the accompanying editorial. For the record: nerve penetration occurred *in vivo* and nerves were not "isolated", in contrast with a previous study [1]; also the needles were not "fine-bore", but standard injection needles.

We examined the consequences of accidental penetration of nerve fascicles and demonstrated that, in this respect, long bevels were superior to short. We agree totally that all efforts should be made to prevent fascicle penetration, and hope all anaesthetists exercise "care" when performing regional anaesthesia, whatever their technique. However, as we stated, there are many other factors involved in needle-induced nerve injury—for example, the ability of different nerve needle bevels to penetrate nerve fascicles in clinical practice. As this area is supported at present only by the type of anecdotal evidence which Baranowski and Buist quote, definitive comment is precluded until substantive data are available. However, it is salutary to note that Sjöström and colleagues [personal communication, 1992] have used long-bevelled needles for more than 17000 supraclavicular blocks, using a paresthesia technique. Eighty percent of their patients were followed up; three cases of serious nerve injury were apparent, but on further investigation they all were found to have resulted from coincidental (surgical) lesions. Dental surgeons have been advised for some years to use long bevelled needles [2].

We cannot be so certain as Baranowski and Buist of detecting nerve fascicle penetration. During microneurography in awake humans [3] when paraesthesiae were elicited, in only a minority of cases was a fascicle impaled (as indicated by a neurographic recording). To be certain that fascicular penetration had occurred, it was necessary to elicit sensations by electrical stimulation at currents of less than 40 µA. The nerve stimulators used in regional anaesthesia are not capable of operating reliably in this range, and are able merely to detect proximity to a nerve trunk [4].

The optimum bevel configuration of needles used in human regional anaesthesia remains to be ascertained.

A. S. C. Rice
S. B. McMahon
John Radcliffe Hospital
Oxford

1. Selander D, Dhuner K-G, Lundborg G. Peripheral nerve injury due to injection needles used for regional anaesthesia. *Acta Anaesthesiologica Scandinavica* 1977; **21**: 182–188.
2. Council on Dental Materials, Instruments and Equipment. ANSI/ADA specification number 54 for double-pointed, parenteral, single use needles for dentistry. *Journal of the American Dental Association* 1986; **113**: 952.
3. Rice A. *Studies in Microneurography*. M.D. Thesis. London: University of London, 1991.
4. Pither C, Raj P, Ford D. The use of peripheral nerve stimulators for regional anesthesia: a review of experimental characteristics, technique and clinical applications. *Regional Anesthesia* 1985; **10**: 49–58.

Sir—It is with great interest that we read the editorial [1] on peripheral nerve damage and we wish to relate to our experience in the prevention of neuropathies after peripheral nerve block. Although a review article [2] suggested that the incidence of neuropathies is small, very serious damage has been reported [3, 4].

We believe that seeking paraesthesiae increases the risk of this type of complication [4, 5], therefore, for the past 2 years, we have been using a nerve stimulator (Pajuncka 861 Germany) which is thought to reduce nerve trauma [6]. Frequency of stimulation is 1 Hz and the intensity generally 0.25 mA for the upper limb and 0.5 mA for the lower limb. We perform regional blocks in conscious, unsedated patients who are not under general anaesthesia. We prefer insulated, short-bevel needles (Stimuplex—Kanüle A, Braun, Germany) rather than pin-point needles, as they enable us better to discern the clearing of the neurovascular sheath in upper limb blocks and in addition, the local anaesthetic is delivered directly onto the nerve. We connect the needle directly to a catheter as recommended by Winnie [7]. The catheter is never filled during the period of seeking the nerve, as we believe that the dispersion of even a small quantity of local anaesthetic near the needle may earth the current, thus inhibiting muscular contractions; above all, it would be dangerous to mask puncture of a nerve [3]. We always prefer to make a single injection of a large volume (30–60 ml) of local anaesthetic (isotonic salt solution, plain 1% lignocaine and 0.5% bupivacaine in a ratio 1:1:1, together, with an opioid (fentanyl or buprenorphine)). I.v. sedation may be administered when the block is complete. For axillary blocks, we prefer to use a single large injection rather than using a "trunk-by-trunk" seeking approach. When this option is chosen, it may be preferable to begin with the most posterior nerves [8].

Since we started following this procedure, we have performed 230 axillary blocks and 80 lower limb blocks with a rate of immediate success of about 86%. We have observed no nerve damage or postanaesthetic dysaesthesiae in the patients. In conclusion, we prefer the axiom "no paresthesia no dysaesthesia" to the outmoded "no paresthesia no anaesthesia" of Moore.

M. E. Gentili
J. P. Wargnier
Clinique Saint Thérèse
Lannion, France

1. Chambers WA. Peripheral nerve damage and regional anaesthesia. *British Journal of Anaesthesia* 1992; **69**: 429–430.
2. Gentili ME, Wargnier JP, Caillon FC. Complications neurologiques périphériques des blocs du plexus brachial. *Cahiers d'Anesthésiologie* 1990; **38**: 561–567.
3. Regnard PJ, Soichot P, Ringuier JP. Accidents locaux de l'anesthésie par blocage axillaire. *Semaine des Hôpitaux de Paris* 1990; **66**: 1601–1605.
4. Selander D, Edshages S, Wolff T. Paresthesiae or no paresthesiae? *Acta Anaesthesiologica Scandinavica* 1979; **23**: 27–33.
5. Plevak DJ, Linstromberg JW, Danielson DR. Paresthesia versus non paresthesia—the axillary block. *Anesthesiology* 1983; **59**: A216.
6. McClain DA, Finucane BT. Interscalene approach to the brachial plexus. Paresthesiae versus nerve stimulator. *Regional Anaesthesia* 1987; **12**: 80–83.
7. Winnie AP. An "immobile needle" for nerve blocks. *Anesthesiology* 1969; **31**: 577–579.
8. Partridge BL, Katz J, Benirsche K. Functional anatomy of the brachial plexus sheath: implications for anesthesia. *Anesthesiology* 1987; **66**: 743–747.

STATISTICAL ASSESSMENT OF TWO METHODS OF CLINICAL MEASUREMENT

Sir,—I read with interest the article by Berridge describing the influence of cardiac output on the correlation between mixed venous and central venous oxygen saturation [1], but was disappointed by its analysis and conclusions. The finding that mixed venous and central venous oxygen saturations measured simultaneously are highly correlated whether cardiac output is small, medium or large does not justify the conclusion that central venous oxygen saturation is a useful estimate of mixed venous oxygen saturation. Such a conclusion requires the appropriate analysis—the Bland–Altman technique for assessing the degree of agreement between two methods of clinical measurement [2]. The deficiencies of the calculation of correlation coefficients in this context are well recognized. A correlation coefficient measures the strength of a relationship between two variables, not the agreement between them. Only agreement between the actual numerical values obtained by the two methods is clinically relevant. If measurements using two different methods are clustered closely around any line (not necessarily the line of equality), they give a high correlation coefficient whether they are in agreement or not. In the circumstances of this study, it is inconceivable that there would not be a strong relationship between mixed venous and central venous oxygen saturations regardless of cardiac output.

In contrast, the Bland–Altman technique directly examines the differences between measurements made using two methods. The first step is to plot the difference between measurements made using two methods against their mean. In this study, the difference between simultaneous mixed venous and central venous oxygen saturations would be plotted against their mean. If there is good agreement between methods of measurement, the mean difference is close to zero with little variability. This graphical technique clearly displays bias (when the mean difference is other than zero). It also shows if differences vary in a systematic way over the range of measurement—that is, if agreement between methods is poorer at larger or smaller values. Further analysis can give limits of agreement, which are the mean difference ± 2 standard deviations of the differences, and their 95% confidence intervals. It is disappointing that the article gave no graphical information; however, the figures in table I do indicate a bias between the two methods of measurement with central venous oxygen saturation consistently greater than mixed venous saturation. Data in table I also suggest that the variability around this bias became wider as cardiac output and mixed venous oxygen saturation decreased. These are precisely the type of insights that a Bland–Altman plot provides and that correlation coefficients can never convey.

The appropriate analysis of the data presented would therefore have been Bland–Altman analysis of the measurements to give a bias and limits of agreement for each of the three groups in the study. Appropriate plots would have indicated clearly if the difference between mixed venous and central venous saturation increased as cardiac output and venous saturation decreased. The extent of acceptable limits of agreement is a clinical decision (usually specified before the study begins) and so it is inappropriate to apply a statistical test to the different limits of agreement for the three groups.

The Bland–Altman technique was first proposed in 1983 [3] and its merits have since been well demonstrated [4, 5]; clear examples of its use have appeared in the standard British anaesthetic journals [6, 7]. It is therefore disappointing to see published a study in which poor choice of statistical technique has fostered inappropriate and misleading conclusions.

C. J. Runcie
Glasgow Royal Infirmary
Glasgow

1. Berridge JC. Influence of cardiac output on the correlation between mixed venous and central venous oxygen saturation. *British Journal of Anaesthesia* 1992; **69**: 409–410.
2. Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet* 1986; 1: 307–310.
3. Altman DG, Bland JM. Measurement in medicine: the analysis of method comparison studies. *Statistician* 1983; 32: 307–317.
4. LaMantia KR, O'Connor T, Barash PG. Comparing methods of measurement: an alternative approach. *Anesthesiology* 1990; 72: 781–783.
5. Murray GD, Miller R. Statistical comparison of two methods of clinical measurement. *British Journal of Surgery* 1990; 77: 384–387.
6. Runcie, CJ, Reeve WG, Reidy J, Dougall JR. Blood pressure measurement during transport: a comparison of direct and oscillotonometric readings in critically ill patients. *Anaesthesia* 1990; 45: 659–665.
7. Andrews PJD, Dearden NM, Miller JD. Jugular bulb cannulation: description of a cannulation technique and validation of a new continuous monitor. *British Journal of Anaesthesia* 1991; 67: 553–558.

Sir,—Thank you for the opportunity to reply. Dr Runcie has correctly stated that correlation is a poor method of determining how closely two methods of measurement agree and I thank him for pointing out this oversight. I therefore provide him with the data he requested, in figure 1. As can be seen, there is a bias, with the central venous sample overestimating the mixed venous. The 95% limits of agreement of that bias are: −0.46 to 7.46% in the small cardiac index group, −3.02 to 9.22% in the medium cardiac index group, −1.59 to 7.19% in the large cardiac index group and −2.6 to 8.8% overall. These limits of agreement are not significantly different between the three groups, suggesting that central venous oxygen saturation as an estimate of mixed venous oxygen saturation is not unduly influenced by cardiac output. It is up to the individual to decide if these limits militate against using central venous oxygen saturation as an estimate of mixed venous oxygen saturation. The reliability of central venous samples to pick up changes in mixed venous oxygen saturation is currently being investigated.

J. C. Berridge
Leeds

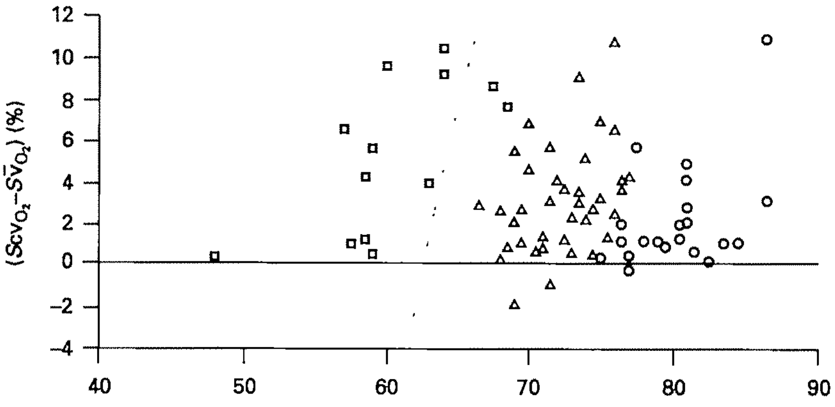


FIG. 1. Bland–Altman plot of difference between central venous and mixed venous oxygen saturation ($Scv_{O_2}-S\bar{v}_{O_2}$) against the mean of the two saturations (($Scv_{O_2}+S\bar{v}_{O_2}$)/2), with small (□), medium (△) and large (○) cardiac index.

CRICOID PRESSURE AND THE LARYNGEAL MASK AIRWAY

Sir,—We read with interest the paper by Ansermino and Blogg [1] on cricoid pressure and insertion of the laryngeal mask airway (LMA). The authors describe a single-blinded randomized, controlled study in which insertion was successful in only three of 20 patients. We were surprised at these results, which are in direct conflict with those of a previous study [2], and we wish to comment further, particularly on the criteria used to assess successful insertion.

Successful placement of the LMA was determined by the presence of all of the following: resistance to continued advancement, outward movement of the LMA on inflation of the cuff, appearance of condensation in the LMA tubing after attachment to the anaesthetic system and gentle manual ventilation with satisfactory compliance. Although all of the above criteria are consistent with successful LMA insertion, we feel that none is a suitable end-point for assessing successful insertion in a clinical trial. The first two criteria fail to demonstrate the final position of the LMA in the hypopharynx. The presence of condensation is difficult to assess in an opaque tube, and perhaps capnography would have been a more reliable technique. The final criterion is subjective and open to considerable interpretation. Furthermore, the authors fail to mention which criteria were not met in those patients in whom LMA insertion was deemed a failure; this information would be of interest in identifying factors producing the poor results with cricoid pressure obtained in this study.

The prerequisite for determining successful insertion is that the LMA provides a clear, functional airway. This usually is dependent on satisfactory placement in the hypopharynx. The position of the LMA is verified easily using a fibreoptic scope passed to the level of the mask aperture bars, and the view obtained may be scored. There are several methods for evaluating function, both subjective and objective, including observation of thoraco-abdominal movement, spirometry and chest transducers. None of the criteria used in this study is a convincing measure of adequate function and they are therefore of questionable value in assessing successful LMA placement, even when taken together.

The role of the LMA in failed intubation requires further elucidation. A recent postmortem study has indicated that, when *in situ*, the LMA does not compromise cricoid pressure [3]. The decision as to whether to use the face mask or the LMA as the first choice alternative to intubation is guided better by studies comparing the two techniques under similar conditions. Ansermino and Blogg suggest that the face mask should be the first choice and the LMA used only as an alternative to cricothyrotomy. We believe that there may be situations in which it would be appropriate for an experienced user to regard the LMA as the best alternative, particularly where difficulty may be anticipated with a face mask. We would also suggest that LMA insertion should be attempted before cricothyrotomy, which carries its own inherent risks.

In an attempt to resolve some of these problems, we are conducting a blinded, randomized, controlled study in which the LMA is inserted in a simulated failed intubation. Successful insertion is judged by function and fibreoptic positioning. The results so far indicate that, whilst insertion is slightly more difficult with cricoid pressure applied, it is successful in 80–90% of patients at the first attempt.

Based on these preliminary findings, and the results of a previous unblinded study in which insertion was successful in 34 of 40 of patients with cricoid pressure applied [2], we feel it is premature to suggest that cricoid pressure should be routinely released, albeit transiently, to allow placement of the LMA in a patient at risk of aspiration.

J. Brimacombe
A. Berry
Royal Perth Hospital
Perth, Australia

1. Ansermino JM, Blogg CE. Cricoid pressure may prevent insertion of the laryngeal mask airway. *British Journal of Anaesthesia* 1992; **69**: 465–467.
2. Brimacombe J. Cricoid pressure and the laryngeal mask airway. *Anaesthesia* 1991; **46**: 986–987.
3. Strang TI. Does the laryngeal mask airway compromise cricoid pressure? *Anaesthesia* 1992; **47**: 829–831.

Sir,—In their paper on cricoid pressure and the laryngeal mask airway [1], Drs Ansermino and Blogg reported that successful insertion was achieved in only three of 20 patients in whom cricoid pressure was applied, compared with 19 of 22 without cricoid pressure. In their discussion of these results they refer to our study [2] as if it had aims (and indeed results) similar to theirs. This is incorrect. Our study assessed ability to intubate blindly through the laryngeal mask. The effects of cricoid pressure were assessed in 50 patients, in all of whom we were able to insert the laryngeal mask satisfactorily (on the simple clinical criterion of easy manual ventilation) during application of cricoid pressure. Our relative lack of success was only in the area of intubation. Thus our results are totally in accord with those of Brimacombe [3], not in contrast as stated by Ansermino and Blogg.

The authors suggested that the lack of skill in insertion of the airway is unlikely to have been a factor in their low success rate with cricoid pressure. They do not comment on their success rate with simulated cricoid pressure (16 of 22 at first attempt, a further three at second attempt, whilst three required removal of the screen). This "success" rate hardly accords with the statement that one of the authors has achieved 648 successful insertions in 10 months (unless he also had 243 failures). We think it far more likely that their experimental design, whilst commendably blind, produced significantly abnormal conditions and that this accounts for the difference between their failure rate (90%, $n = 20$) and that of ourselves and Brimacombe combined (3%, $n = 90$).

We disagree with the authors' conclusions on the utility of the laryngeal mask in patients for whom cricoid pressure is indicated. Our view is supported by the excellent study of Strang [4] which demonstrated that the presence of the laryngeal mask does not compromise the effectiveness of cricoid pressure.

M. L. Heath
J. Allagain
Lewisham Hospital
London

1. Ansermino JM, Blogg E. Cricoid pressure may prevent insertion of the laryngeal mask. *British Journal of Anaesthesia* 1992; **69**: 465–467.
2. Heath ML, Allagain J. Intubation through the laryngeal mask. *Anaesthesia* 1991; **46**: 545–548.
3. Brimacombe J. Cricoid pressure and the laryngeal mask airway. *Anaesthesia* 1991; **46**: 986–987.
4. Strang TI. Does the laryngeal mask airway compromise cricoid pressure? *Anaesthesia* 1992; **47**: 829–831.

Sir,—Thank you for the opportunity to reply to Dr Heath and Mr Allagain. We could not compare their uncontrolled study directly with our randomized, prospective, comparative and blinded study as their paper [1] did not give details of the successful placement of the laryngeal mask airway (LMA) before they attempted blind intubation, and merely described the success in placing a tracheal tube. In support of our findings that application of cricoid pressure before insertion of the LMA may prevent accurate placement of the LMA, we quoted their failure in 22 of 50 patients to place the tube without release of the cricoid pressure. It is salutary also to record their relative lack of success in this group (44%) in whom cricoid pressure was applied, compared with 90% in those patients who did not have cricoid pressure applied. Despite the unblinded design of their studies, such a marked difference ($P < 0.005$, χ^2 3.95) surely supports our view that cricoid pressure interferes with the placement of the LMA, as that was the only methodological difference between their groups. Indeed, Heath and Allagain themselves state that "momentary relaxation of cricoid pressure during placement of the mask and again during the intubation manoeuvre will provide the best compromise between protection against regurgitation during the procedure and rapid successful intubation".

If our success rate in placing an LMA should be compared with the combination of their's [1] and that from another continent carried out in a different manner [2], then it will be noted that in *all* of our 42 patients the LMA was placed successfully whereas, in the combined series, in 28 of 90 patients intubation could not be achieved whilst cricoid pressure was applied. Further, in three patients the LMA could not be positioned satisfactorily within 1 min, resulting in abandonment of the attempted intubation.

The failure to pass the tube or the LMA successfully may be the result of several factors. Heath and Allagain suggest themselves that cricoid pressure encourages "downfolding" of the epiglottis sufficient to allow unsatisfactory intubation. Difficulties in accurately judging placement of the LMA, or tube, are illustrated further by their suggestion that intubation could be unsatisfactory "despite clear evidence of the tube being placed within the respiratory pathway". Practised users of the LMA will appreciate that simply relying upon ability to inflate the lungs via a LMA is no guarantee of its accurate placement, as the LMA may achieve an air-tight seal despite sitting above the larynx—hence our reliance on a battery of tests to confirm the placement.

It should be noted also that the presence of the screen in our blinded series did not hinder placement of the LMA. The screen was removed before successful placement in three of our patients because observation of the patient's clinical condition was obscured in two and its presence impeded use of a laryngoscope in the third.

Heath and Allagain further confuse the problem by quoting the study by Strang [3], in which the efficacy of the LMA was tested in cadavers in whom the LMA had been inserted *before* application of cricoid pressure, and the ability to inflate the lungs was not reported. Our experience of studying the use of the LMA in cadavers leads us further to believe that the anatomical differences reduce the applicability of the information obtained.

We stand by our conclusion that cricoid pressure may prevent accurate placement of the LMA and, if there is significant risk of regurgitation, it may be better if a tracheal tube cannot be passed, to maintain cricoid pressure rather than to release it in those patients in whom accurate placement may be prevented.

C. E. Blogg
Radcliffe Infirmary
Oxford
J. M. Ansermino
University of the Witwatersrand
Johannesburg, South Africa

1. Heath ML, Allagain J. Intubation through the laryngeal mask. *Anaesthesia* 1991; **46**: 545–548.
2. Brimacombe J. Cricoid pressure and the laryngeal mask airway. *Anaesthesia* 1991; **46**: 986–987.
3. Strand TI. Does the laryngeal mask compromise cricoid pressure? *Anaesthesia* 1992; **47**: 828–831.

LAPAROSCOPIC *VS* OPEN CHOLECYSTECTOMY

Sir,—We read with interest the paper by Joris and colleagues [1]. It is widely reported that patient recovery is more rapid after laparoscopic than after open cholecystectomy. The biochemical basis of this remains to be determined. This study adds further to the weight of evidence demonstrating a reduction in the acute phase response after laparoscopic cholecystectomy. Mealy and colleagues [2] also documented significantly smaller C-reactive protein concentrations after laparoscopic compared with open cholecystectomy.

We have conducted a similar study in 25 patients undergoing elective cholecystectomy [3]. Mean interleukin-6 concentrations peaked at 4 h after surgery (57.2 and 99.3 pg ml^{-1} in the laparoscopic and open groups, respectively ($P < 0.01$)). Mean C-reactive protein concentrations at 24 h were 17 and 49 mg litre^{-1} and at 48 h after operation were 28 and 70 mg litre^{-1} in the laparoscopic and open groups, respectively ($P < 0.01$).

We also assessed recovery of our patients in the 48 h after operation, using subjective fatigue scores and voluntary hand grip strength. The mean fatigue scores of both groups at 24 h after surgery were significantly greater than the values before operation ($P < 0.05$). The mean fatigue score of the laparoscopic patients at 48 h had returned to the preoperative value, whilst that of the open cholecystectomy patients remained significantly increased and was significantly greater than that of the laparoscopic group ($P < 0.05$). Voluntary hand grip strength was reduced significantly only after open cholecystectomy, and only at 24 h after operation ($P < 0.05$). A similar pattern of fatigue and impairment of voluntary muscle strength in the patients studied by Joris and colleagues may have contributed to the impairment of pulmonary function which they identified.

We extended our study of patient recovery to include the first 1 month after discharge from hospital. Patients were requested to complete questionnaires, detailing fatigue sensation, pain and actual daily activities, at 1-week intervals for 4 weeks. Preliminary findings would suggest that laparoscopic patients remain pain free in the 2–3 weeks after discharge. However, during this period there appears to be a trend for their mean fatigue score to increase to greater than that recorded before operation. Thus it is possible that a cohort of patients undergoing laparoscopic cholecystectomy may develop a fatigue syndrome during the postoperative period, similar to that which may occur after laparotomy [4] and which has, as yet, not been recognized.

It is reasonable to speculate that the reduction in the acute phase response, possibly caused by reduced tissue trauma [5], is linked to early recovery after laparoscopic cholecystectomy. Christensen and Kehlet [6], have shown that postoperative fatigue is not predictable from preoperative nutritional status and that it does not correlate with postoperative changes in haemoglobin, albumin, electrolytes or various minerals. The role of cytokine activity in postoperative recovery and fatigue has not been investigated specifically, although evidence now available suggests that this is worth pursuing. However, this will necessitate controlled studies continuing for several weeks into the postoperative period.

M. S. R. Jakeways
F. Carli
Clinical Research Centre
Harrow

1. Joris J, Cigarini I, Legrand M, Jacquet N, De Groote D, Franchimont P, Lamy M. Metabolic and respiratory changes after cholecystectomy performed via laparotomy or laparoscopy. *British Journal of Anaesthesia* 1992; **69**: 341–345.
2. Mealy K, Gallagher H, Barry M, Lennon F, Traynor O, Hyland J. Comparison of the physiological responses to open and laparoscopic cholecystectomy. *British Journal of Surgery* 1992; **79**: 1061–1064.
3. Jakeways MSR, Mitchell V, Hashim IA, Chadwick SJD, Anderson J, Carli F, Shenkin A. Metabolic and inflammatory changes following laparoscopic cholecystectomy. *Proceedings of the Nutrition Society* 1993; (in press).
4. Christensen T, Bendix T, Kehlet H. Fatigue and cardiorespiratory function following abdominal surgery. *British Journal of Surgery* 1982; **69**: 417–419.
5. Cruickshank AM, Fraser WD, Burns HJG, Van Damme J, Shenkin A. Response of serum interleukin-6 in patients undergoing elective surgery of varying severity. *Clinical Science* 1990; **79**: 161–165.
6. Chrisensen T, Kehlet H. Postoperative fatigue and changes in nutritional status. *British Journal of Surgery* 1984; **71**: 473–476.

COMBINED CAFFEINE–HALOTHANE TEST FOR MALIGNANT HYPERTHERMIA

Sir,—The article by Halsall and Hopkins [1] examined the value of the combined caffeine–halothane test for malignant hyperthermia (MH) and in the process questioned many issues surrounding MH diagnostic contracture testing. I manage an MH diagnostic centre that has used the combined caffeine–halothane contracture test involving nearly 400 patients. We initially referred to positive responders as "K" phenotypes [2] because Kalow (with Britt and Chan) originally described the population [3]. I continue to use this controversial test because I believe that MH is genetically heterogenous in humans; that, individually, halothane or caffeine tests may not identify all MH-susceptible probands; and that generation of false positives is more desirable than production of a population of false negatives—that is, all susceptible relatives of all falsely diagnosed MH-susceptible probands.

There are several disturbing aspects of the report by Ellis' group that should be questioned. First, it must be pointed out that, in contrast to the North American MH diagnostic procedure [4, 5], the European procedure has not been scrutinized analytically among and within diagnostic centres and there are no scientific data available to assess the sensitivity or specificity of these tests. Only two fascicles are used for each of the standard tests, and only one fascicle was used for the caffeine–halothane test. Would the diagnostic outcome be different if three fascicles instead of two were used in the European procedure (as per the North American procedure)? Certainly, the use of only one fascicle per patient for the caffeine–halothane test is inadequate for the hypothesis testing attempted in this study. The presentation of the data in table I is biased and misleading, as is discussion of the issues within the text. There is no scientific basis of proof that the K responders in the MHN group are truly MH negative. From the data presented in table I, it is inferred that the combined caffeine–halothane test results in a false negative rate of 45 %. Also, the authors stated that "the CHCT can produce both false positive and false negative results... and is potentially dangerous." Preceding these statements, they observed that exposure to 1 % halothane produced large contractures and that, following this, the contracture response to caffeine did not exceed 1 g. The authors declared this as an MH-negative response for the CHCT test. They stated, "It is questionable if the CHCT should be classed as negative in this situation," but then present the data and discuss it in a very biased manner. To skew the data by interpreting these responses as negative is scientifically unsound and unjustified.

I believe that the time has come for all who deal with this disease to realize that it is a complex process, predisposed by mutations that can differ from one family to another [6] and by environmental factors that we do not yet understand. If we believe that existing diagnostic tests are truly sensitive and specific, then we deceive ourselves. What if we were to limit diagnostic tests to only the *in vitro* contracture responses of muscle from patients who have developed the "malignant syndrome"? We would exclude some families who are also predisposed, perhaps less profoundly so, but still to an extent that could be life-threatening. An open-minded, objective evaluation of malignant hyperthermia must be maintained in order to advance our knowledge and understanding of this disease.

T. E. Nelson
Bowman Gray School of Medicine
Winston-Salem, NC, U.S.A.

1. Ellis FR, Halsall PJ, Hopkins PM. Is the "K-type" caffeine–halothane responder susceptible to malignant hyperthermia? *British Journal of Anaesthesia* 1992; **69**: 468–470.
2. Nelson TE, Flewellen EH, Gloyna DF. Spectrum of susceptibility to malignant hyperthermia—diagnostic dilemma. *Anesthesia and Analgesia* 1983; **62**: 545–552.
3. Kalow W, Britt BA, Chan FY. Epidemiology and inheritance of malignant hyperthermia. *International Anesthesiology Clinics* 1979; **17**: 119–139.
4. Larach MG. Standardization of the caffeine halothane muscle contracture test. North American Malignant Hyperthermia Group. *Anesthesia and Analgesia* 1989; **69**: 511–515.
5. Larach MG, Landis JR, Shirke BS, Diaz M. Prediction of malignant hyperthermia susceptibility in man: improving sensitivity of the caffeine halothane contracture test. *Anesthesiology* 1992; **77**: A1052.
6. Levitt RC. Prospects for the diagnosis of malignant hyperthermia susceptibility using molecular genetic approaches. *Anesthesiology* 1992; **76**: 1039–1048.

Sir,—We agree with many of the points raised in Dr Nelson's letter. There is now no doubt that MH is heterogeneic. Within the European population, there are more families who do not show linkage with the RYR gene on chromosome 19 than do. Also, the so-called "pig-mutation" is not a feature of human MH.

What is surprising is the continued value of the halothane (and the caffeine) contracture tests, even though in different families different genes are responsible for the transmission of MH susceptibility (MHS).

With the halothane-caffeine combined contracture test (CHCT), abnormal results are obtained in more than 10 % of the population. Clearly, therefore, the combined test cannot be specifically predicting MHS, which we know to be a comparatively uncommon state, about 1 in 8000 of the population. If human MH were a recessive characteristic (as it appears to be in the pig) an incidence of 10 % might be reasonable. However, within the families, the distribution of MHS individuals shows the MH gene clearly to be dominant. Thus there seems to be no rationale for the caffeine–halothane combined test in MH screening.

It is difficult to see how to display our data, except as in table I. It is apparent that there is controversy about the interpretation of the results of the CHCT. We followed that described by Melton and co-workers [1], who described the test as positive if 1 g of tension was reached after the addition of caffeine. If an alternative interpretation is taken to be a total of 1 g increase in tension from the predrug tension, the number of normal CHCT results in otherwise MHS patients may decrease. The North American MH group procedure has not attempted to define the limits of the CHCT [2]. In the light of this difference in interpretation, we have reassessed the results and find that the negative CHCT was reduced from 10 to four in MHS patients and from six to five in MHE(h) patients. This alteration in the interpretation of the results does not affect the MHN group.

The validity of the European Group's procedure was presented in our discussion, although formal "analytical scrutiny" has not been performed among all the European diagnostic centres. However, all the larger centres have control data and the diagnostic procedures in Leeds have stood the test of more than 20 years and more than 2500 biopsies. Perhaps that is more valid than analytical scrutiny of a few results.

In order to substantiate a different type of MH-susceptible patient characterized by the K-type, a clear demonstration of its inheritance through the family is needed if Dr Nelson's view is to retain any credibility.

F. R. Ellis
P. J. Halsall
P. M. Hopkins
St James's University Hospital Trust
Leeds

1. Melton AT, Martucci RW, Kien ND, Gronert GA. Malignant hyperthermia in humans—standardisation of contracture testing protocol. *Anesthesia and Analgesia* 1989; **69**: 437–443.
2. Larach M. Standardisation of the caffeine halothane muscle contracture test. *Anesthesia and Analgesia* 1989; **69**: 511–515.

SPIN RESONANCE SPECTROSCOPY TO DETECT MALIGNANT HYPERTHERMIA SUSCEPTIBILITY

Sir,—We note the results reported in the paper by Halsall, Ellis and Knowles [1] and those reported in another recent study of malignant hyperthermia (MH) [2]. Both studies attempted to reproduce the results of an MH study of Ohnishi and colleagues [3]. The first concluded, from a study of 10 MH-susceptible (MHS) and nine MH-normal (MHN) patients, that there was no significant difference in the fluidity of red blood cell membranes from the two groups. The second concluded, from a study of six MHS and six MHN volunteers, that a significant difference ($P < 0.001$) existed between their two groups both with and without fluidization using halothane. Both studies measured the rotational correlation time (τ_r) of the 16-deoxylstearic acid spin label at 37 °C using 9-GHz electron paramagnetic resonance (EPR) spectroscopy. There appear to be several important factors that should be examined.

The sample preparation procedures were similar but not identical. Initially, Cooper and colleagues [2] attempted to produce spin-labelled erythrocyte samples using the method of Ohnishi and colleagues [3]. However, EPR spectra were not observed, so they developed a revised method [2]. It can be concluded that this method of Ohnishi and colleagues [3] resulted in spin-label:lipid ratios which were sufficient to induce significant erythrocyte (red blood cell) membrane perturbations. This conclusion is in agreement with the observation that the τ_r values reported [3] are inconsistent with the hypothesis that MHS erythrocyte membranes should be more fluidized than MHN membranes. The procedure of Cooper and colleagues [2] led to values that were consistent with this hypothesis, although the differences were not significant; they ascribed this to the fact that it is very difficult to fluidize samples consistently and accurately using halothane. They estimated that their method resulted in spin-label:lipid ratios that did not exceed 1:100, so the membranes were not perturbed significantly, in agreement with a electron microscopic study [4]. It is suggested that use of the method of Ohnishi and colleagues by Halsall and colleagues [1] also resulted in significant membrane perturbation.

No information concerning the repeatibility of EPR spectral analysis measurements was given by Halsall and colleagues [1] or Cooper and colleagues [2]. The latter used a digital data

TABLE I. *Mean* (SEM) *rotational correlation times* (τ_r) *for the MHS and MHN sample groups with fluidization produced by various concentrations of halothane* [1, 2] *and benzyl alcohol* [2]

	Rotational correlation time (ns)			
Fluidizer concentration (mmol litre^{-1})	Reference [1]		Reference [2]	
	MHS	MHN	MHS	MHN
Halothane				
0	3.722 (76)	3.642 (80)	2.139 (12)	2.223 (13)
0.3	—	—	2.118 (10)	2.192 (8)
1.0	—	—	2.103 (9)	2.180 (4)
3.0	3.647 (90)	3.794 (108)	2.067 (12)	2.172 (5)
Benzyl alcohol				
25	—	—	2.079 (11)	2.170 (16)
50	—	—	2.002 (18)	2.111 (18)

acquisition system which resulted in 1200 data points over the 10-mT magnetic field sweep width. The precision for individual measurements could be improved from approximately 0.5% to approximately 0.1% by the introduction of the software program which was developed. This precision was determined by repeating the analysis several times and by using different analysts. This experience leads to the conclusion that the precision achieved by Halsall's group [1] using a set-square and calipers to measure a spectrum could not exceed 0.5%, and probably 1% is more realistic. Moreover, the signal-to-noise ratio achieved by Cooper's group [2] was approximately 300:1, whereas it was approximately 100:1 Halsall's group [1]. This also contributed to the precision achieved by the former, who used a blind sample labelling procedure to remove bias concerning the sample group membership. Halsall and colleagues [1] reported that the τ_r values were very sensitive to small changes in the central line width (W_0), whereas Cooper and colleagues [2] found that W_0 was essentially independent of the degree of fluidization.

Both studies [1, 2] assessed the statistical significance of the mean τ_r values for the MHS and MHN sample groups using the Mann–Whitney *U* test, and agree that no significant differences were attributable to halothane or benzyl alcohol, contrary to the conclusion of Ohnishi and colleagues [3]. However, Cooper and colleagues [2] found that the differences between the mean τ_r values for the MHS and MHN sample groups were significant for all concentrations of each of the two membrane fluidizing agents. It is evident from the data of Halsall and colleagues [1] that there was no significant difference between the MHS and MHN sample groups for both halothane concentrations within the SEM values for each group.

Table I summarizes the mean (SEM) values of the rotational correlation times (τ_r) for the MHS and MHN sample groups with halothane 0, 0.3, 1.0 and 3.0 mmol litre^{-1} [1, 2] and with benzyl alcohol 0, 25 and 50 mmol litre^{-1} [2]. The SEM values of Halsall and colleagues [1] are more than six times those of Cooper and colleagues [2], in agreement with the measurement precision estimates discussed above.

It is concluded that erythrocyte membranes are a good proxy for skeletal muscle membranes. This suggests that MH may be a symptom of a generalized membrane defect, contrary to general belief and other evidence [5].

H. A. BUCKMASTER
K. A. KERR
J. KUDYNSKA
University of Calgary
Calgary, Canada

ACKNOWLEDGEMENTS

This research was proposed by Dr A. K. Brownell and supported by an operating grant (A0716) awarded by the Natural Sciences and Engineering Research Council of Canada to one of us (H.A.B.). Dr P. Cooper was responsible for developing the spin-label recipe and for collecting and labelling the samples and Dr T. H. T. van Kalleveen was responsible for the development of the software programs that played a major role in the data analysis.

1. Halsall PJ, Ellis FR, Knowles PF. Evaluation of spin resonance spectroscopy of red blood cell membranes to detect malignant hyperthermia susceptibility. *British Journal of Anaesthesia* 1992; **69**: 471–473.
2. Cooper P, Kudynska J, Buckmaster HA, Kudynski R. An EPR investigation of spin-labelled erythrocytes as a diagnostic technique for malignant hyperthermia. *Biochemica et Biophysica Acta* 1992; **1139**: 70–76.
3. Ohnishi ST, Katagi H, Ohnishi T, Brownell AKW. Detection of malignant hyperthermia susceptibility using a spin-label technique on red blood cells. *British Journal of Anaesthesia* 1988; **61**: 565–568.
4. Bieri VG, Wallach DFH, Lin PS. Focal erythrocyte membrane perturbations caused by nitroxide lipid analogues. *Proceedings of National Academy of Sciences U.S.A.* 1974; **71**: 4797–4801.
5. Cooper P, Meddings JB. Erythrocyte membrane fluidity in malignant hyperthermia. *Biochemica et Biophysica Acta* 1991; **1069**: 151–156.

Sir,—Thank you for the opportunity to reply to the letter by Buckmaster and colleagues, which we found difficult to follow. The crux of the matter is that, whereas our studies indicate no difference within the limits of error between normal and MH-susceptible patients for the fluidity of erythrocyte membranes, the data of Cooper and colleagues [1] indicate a small but significant difference. Buckmaster and colleagues criticize our work with respect to sample preparation, electron paramagnetic resonance (EPR) spectral analysis and statistical analysis of the data.

Taking these points in turn, our sample preparation attempted to reproduce that used by Ohnishi and colleagues [2]. Unlike Cooper and colleagues [1], we had no difficulty obtaining spin labelling of erythrocyte membranes by this procedure. Our spin labels (16-deoxylstearic acid 1 mol/100 mol membrane lipid) are unlikely to have induced any membrane perturbation [3].

Our EPR data collection procedure is closely similar to that of Cooper and colleagues [1]; both involve digital acquisition of 1200 data points over a 100-mT magnetic field sweep. Determination of the rotational correlation time from the spectra both in our studies and in those of Cooper is based on the method of Keith, Bulfield and Snipes [4].

We analysed the spectra manually, whereas Cooper and colleagues [1] determined their correlation time using computer analysis of the acquired digital data. The latter is clearly superior. Both the Leeds and the Calgary studies used a blind sample procedure to remove bias and the statistical analysis procedures were the same.

On balance, the most likely explanation for the difference in results obtained in Leeds and Calgary lies in the determination of the rotational correlation time from the EPR data. We will use the amended EPR analysis procedure suggested by Cooper and colleagues [1] to re-examine this matter. It is important that it be resolved, because of the implications of a generalized membrane defect in MH.

P. J. HALSALL
F. R. ELLIS
P. F. KNOWLES
University of Leeds
Leeds

1. Cooper P, Kudynska J, Buckmaster HA, Kudynski R. An EPR investigation of spin-labelled erythrocytes as a diagnostic technique for malignant hyperthermia. *Biochemica et Biophysica Acta* 1992; **1139**: 70–76.
2. Ohnishi ST, Katagi H, Ohnishi T, Brownell AKW. Detection of malignant hyperthermia susceptibility using a spin label technique on red blood cells. *British Journal of Anaesthesia* 1988; **61**: 565–568.
3. Marsh D, Watts A, Pates RD, Uhl R, Knowles PF, Esnanu M. ESR spin-label studies of lipid–protein interactions in membranes. *Biophysical Journal* 1982; **37**: 265–274.
4. Keith A, Bulfield G, Snipes W. Spin-label neurospora mitochondria. *Biophysical Journal* 1970; **10**: 618.

THE AIRWAY DECIDES THE ANAESTHETIC APPROACH BEFORE TRACHEAL INTUBATION

Sir,—The review by Cobley and Vaughan [1] dealt with difficult intubation, rather than difficult airways, and therefore seemed incorrectly titled. "Difficult airway" and "difficult intubation" do not always, or necessarily, occur together and they are not synonymous and interchangeable [2]. In the absence of pre-existing compromise of the airway, or its control and maintenance, inability to see the glottis with a laryngoscope does not automatically translate to, or equate with, a "difficult airway" being present. In practice, such an association is uncommon.

The tracheal tube is *an* airway, but not *the* airway. Whilst failure to intubate may delay surgery temporarily, failure to maintain the airway, and oxygenation, can cause serious or lethal damage to the patient. Cerebral damage or death are the sequelae, not of "inadequately managed difficult intubation" [1], but of the inadequately managed, or lost, airway. Careful preoperative assessment is the best method of avoiding disaster [1] because it predicts potentially difficult airways rather than because it predicts "difficult" intubations [1]. Signs of the first are amongst those usually used for the second. Some form of anaesthesia is usually required before tracheal intubation. The decision to use i.v., inhalation or awake local anaesthesia is dictated by assessment and difficulty of the airway, as is the anaesthetic approach to the compromised airway [3]. The choice should err on the safe side and will reflect the anticipated ability (or not) to control or retain the airway with a particular approach. The decision on the airway must be made before induction of anaesthesia. Using i.v. induction agents in sleep doses for insertion of a tracheal tube [4] or laryngeal mask [5, 6] when airway control is compromised and uncertain carries considerable risk if the placement of the device proves unsuccessful or difficult.

The value of transtracheal ventilation and of retrograde intubation, especially for the inexperienced, is that they circumvent airway and intubation problems and are possible in the awake patient. Awake intubation is necessitated, not by intubation, but by airway considerations. It seems misused and overused.

Cobley and Vaughan [1] could also have mentioned ketamine and topical anaesthesia in the young [7, 8], nasopharyngeal airways and the possible relevance of the sleep history.

R. Williamson
University of Natal
Congella, South Africa

1. Cobley M, Vaughan RS. Recognition and management of difficult airway problems. *British Journal of Anaesthesia* 1992; **68**: 90–97.
2. Williamson R. Endotracheal intubation in temporomandibular ankylosis. *Anesthesia and Analgesia* 1988; **67**: 602–603.
3. Donlan JV. Anesthesia for eye, ear and throat surgery. In: Miller RD, ed. *Anesthesia*. New York: Churchill Livingstone, 1981; 1265–1321.
4. Fry ENS. Difficult tracheal intubation. *Anaesthesia* 1985; **40**: 206–207.
5. Calder I, Ordman AJ, Jackowski A, Crockard HA. The Brain laryngeal mask airway. *Anaesthesia* 1990; **45**: 137–139.
6. Chadd GD, Ackers JWL, Bailey PM. Difficult intubation aided by the laryngeal mask airway. *Anaesthesia* 1989; **44**: 1015.
7. Smith BL. Anaesthesia and Still's disease. *Anaesthesia* 1985; **40**: 209.
8. Kleeman PP, Jantzen JPAH, Bonfils P. The ultra-thin bronchoscope in management of the difficult paediatric airway. *Canadian Journal of Anaesthesia* 1987; **34**: 606–608.

Sir,—We thank you for the opportunity to reply.

Most anaesthetists when faced with "the difficult airway" would, in our experience, try to secure that airway with a tracheal tube. The title of our article was therefore chosen with this broad principle in mind. However, we accept that "difficult intubation" would have been more appropriate.

R. S. Vaughan
M. Cobley
University Hospital of Wales
Cardiff

PAIN RELIEF AFTER ANTERIOR CRUCIATE LIGAMENT REPAIR

Sir,—Dr Joshi and colleagues are to be commended for emphasizing the problem of severe pain after knee surgery and for describing their technique of intra-articular morphine infusion [1]. We agree that both PCA and continuous neuraxial infusions are not ideal in this situation.

However, we would have included local anaesthetic neural block in our list of postoperative analgesic alternatives. Both the sciatic and the femoral nerves can be located reliably and blocked with the aid of a nerve stimulator. The duration of high quality analgesia thus obtained frequently exceeds 24 h.

Perhaps, as we enter the age of "pre-emptive analgesia", lower limb peripheral nerve block will begin to receive the attention it deserves.

P. H. Carroll
J. G. Allen
Queen Elizabeth Hospital
Kings Lynn

1. Joshi GP, McCarroll SM, Brady OH, Hurson BJ, Walsh G. Intra-articular morphine for pain relief after anterior cruciate ligament repair. *British Journal of Anaesthesia* 1993; **70**: 87–88.

Sir,—Thank you for the opportunity to reply to the letter from Drs Carroll and Allen. The aim of our study was a clinical evaluation of the effectiveness of intra-articular morphine in relieving acute pain in the early postoperative period after anterior cruciate ligament (ACL) repair [1]. We agree that the use of peripheral neural block can be considered an alternative method of postoperative analgesia after ACL repair.

Recently, peripheral blocks have attracted attention as there is now substantial evidence that pre-emptive analgesia diminishes postoperative pain and requirements for supplementary analgesics [2, 3]. Continuous lumbar plexus block has been shown to be effective in patients undergoing open knee surgery [4, 5]. However, the placement of a catheter into the perineural space requires skill and experience. It is time-consuming, and may not be agreeable to all patients. It also has the disadvantage of producing motor block which can delay ambulation. Intra-articular injection of morphine is a simple and safe technique which does not require any special skill or equipment.

G. P. Joshi
University of Texas
Dallas, Texas

1. Joshi GP, McCarroll SM, Brady OH, Hurson BJ, Walsh G. Intra-articular morphine for pain relief after anterior cruciate ligament repair. *British Journal of Anaesthesia* 1993; **70**: 87–88.
2. Katz J, Kavanagh BP, Sandler AN, Nierenberg H, Boylan JF, Friedlander M, Shaw BF. Pre-emptive analgesia. Clinical evidence of neuroplasticity contributing to postoperative pain. *Anesthesiology* 1992; **77**: 439–446.
3. Ejlersen E, Andersen HB, Eliasen K, Mogensen T. A comparison between preincisional and postincisional lidocaine infiltration and postoperative pain. *Anesthesia and Analgesia* 1992; **74**: 4950–4958.
4. Schultz P, Anker-Moller E, Dahl JB, Christensen EF, Spansberg N, Fauno P. Postoperative pain treatment after open knee surgery: Continuous lumbar plexus block with bupivacaine versus epidural morphine. *Regional Anesthesia* 1991; **16**: 34–37.
5. Serpell MG, Millar FA, Thomson FM. Comparison of lumbar plexus block versus conventional opioid analgesia after total knee replacement. *Anaesthesia* 1991; **46**: 275–277.

British Journal of Anaesthesia 1993; 70: 601

BOOK REVIEWS

The Oxford Textbook of Clinical Pharmacology and Drug Therapy, 2nd Edn. By D. G. Graham-Smith and J. K. Aronson. Published by Oxford University Press, Oxford. Pp. 756; indexed; illustrated. Price £17.50.

This textbook, written primarily for undergraduates, was first published in 1984. In this new edition, the main change has been the inclusion of a large number of invited contributions from "specialists" on the drug treatment of disease. The book is laid out in four sections comprising the scientific basis of drug therapy, prescribing, the drug treatment of disease and a pharmacopoeia. More than 70% of the book is concerned with the scientific basis of drug therapy and the drug treatment of disease. It is produced as a laminated hardback and should prove sufficiently durable for the majority of students.

The opening section on pharmacological principles is a model of clarity and can be recommended without reservation to all medical students and to those preparing for the Part 2 Anaesthetic Fellowship examinations of the Royal Colleges. The drug treatment of disease is, for the most part, comprehensive and will serve as a useful reference. Unfortunately, a few myths are perpetuated and whereas some of these are simply amusing, others are positively dangerous. It is, of course, a fallacy to believe that, in the treatment of drug overdose, hypoxaemic patients should be given "24% oxygen increasing to 28% oxygen after 30 minutes if the alveolar carbon dioxide tension has not risen". This is nonsense, and simply will not do!

It is also very disappointing that the opportunity was not taken to provide a section dealing with the drug management of chronic pain. It is widely recognized that this common problem receives scant attention in the medical curriculum and this book has failed those who are trying to remedy the situation. The treatment of intractable pain in terminal malignancies is covered in half a page and that of a few other chronic pain syndromes is covered superficially in different chapters.

The chapter on general anaesthesia and local anaesthetics is a worthwhile introduction to the subject.

It is perhaps inevitable, in a book written by clinical pharmacologists, that the emphasis should be on the drug management of what have traditionally been considered medical conditions. For example, inotropic drugs are discussed mostly in terms of their use after myocardial infarction and there is very little mention of their role in the management of trauma or endotoxaemia. Similarly, the use of non-steroidal anti-inflammatory drugs for the treatment of arthritic conditions is covered comprehensively, but there is only the most superficial mention of their role in postoperative pain management. Patient-controlled analgesia systems are ignored.

This new edition has attempted, like its predecessor, to bridge the gap between pharmacology and the clinical management of disease states. In general it has succeeded, but it is not sufficiently comprehensive or authoritative to warrant an unreserved endorsement for topics outside the field of internal medicine.

J. P. H. Fee

Handbook of Percutaneous Central Venous Catheterisation, 2nd Edn. Edited by M. Rosen, P. Latto and S. Ng. Published by W. B. Saunders Co., Ltd, London, Philadelphia, Toronto, Sydney, Tokyo. Pp. 249; indexed; illustrated. Price £19.95.

This is the second edition of a book which was very well received when it appeared 9 years ago. Its format is very close to the original. The first part of the book describes the indications for the insertion of catheters. Each separate section gives an outline description of a different method. The dangers and complications are mentioned and in most cases the frequency is given at which such complications occurred in a published series.

Each section is accompanied by a comprehensive list of references. Many of these are not of recent date, but this may just indicate that there is nothing new to say about the indications for, and complications of, i.v. catheter placement.

Part 2 of the book is devoted to cannulation and catheterization in infants. This is a particularly useful section.

The illustrations form a major part of the book. The line diagrams are much better than the photographs and some of the x-rays are of limited value, as they are used simply as backgrounds upon which lines are drawn to indicate incorrect and correct position of catheters.

Inevitably, there are some techniques described which are such that one can only be tempted to think, why was this method attempted? The Editors give clear preference to some of the techniques, based upon their own experience.

Although I do not believe that a complete tyro could become competent after reading this book, there are some very useful hints in it which can be read with benefit by even the most experienced.

In summary, I believe this book has become the Bible of the cannulist and will continue to be as popular.

J. C. Stoddart

Electrical Trauma: the Pathophysiology, Manifestations and Clinical Management. Edited by R. C. Lee, E. G. Cravalho and J. F. Burke. Published by Cambridge University Press, Cambridge, New York. Pp. 440, indexed; illustrated. Price £65.00.

Three American professors (two surgeons and a medical engineer) have led a team of 31 contributors to produce a book the stated aim of which is to be a comprehensive review of the pathophysiology and clinical manifestations of electrical trauma. They have succeeded admirably, with the technical chapters in the latter half of this book being jewels of considerable clarity.

The book is subdivided into four sections: the introductory three chapters in Part I provide a historical review which includes a useful résumé of basic electrical physics, a summary from the national electrical supply company of France of the investigation of electrical accidents over 40 years, and an excellent chapter presenting an overview of the pathophysiology and clinical management of electrical injury. Part II offers, from a broad range of United States Burns Units, nearly 100 pages on how to look after these patients who comprise a significant proportion (5%) of admissions. The book then turns, in parts III and IV, to the cellular aspects of these injuries, entitled "Tissue responses" and "Biophysical mechanisms of cellular injury". I cannot comment on the merits of the physics contained in these latter 20 chapters, but it is sufficient to say that each undoubtedly gives an up-to-date review in its respective field.

From the viewpoint of a burns surgeon, there are many welcome teaching points included within this book: the importance of "hidden damage" between the entrance and exit wounds which is often missed in electrical burns extending between the upper and lower limbs; the value of the "empirical" fasciotomy in patients with high-voltage injuries of the upper limb (and not just the hand) before signs of compartment syndrome are evident (this is one time when anaesthesia is necessary for a burns fasciotomy, unlike thermal burns); the awareness of the occurrence of skeletal fractures and joint dislocations as a result of tetanic contractions. There are many more.

As one might expect from a book with an almost entirely transatlantic list of contributors, there are details with which I could disagree. In the United Kingdom we do not routinely use allografts to cover decompressed viable muscle during serial debridements, relying often on antiseptic dressings, and I would use systemic antibiotics rather than a topical antimicrobial as prophylaxis against *Clostridium* infection. There are also differences in our National Grid which negate many of the figures given for transmission and distribution voltages.

These points, however, do not detract from the value of this book. I can confirm the publisher's claim that it is suitable for clinicians in trauma surgery, accident medicine, plastic surgery, intensive care and burns units, and recommend it wholeheartedly as a reference book for the library in any of these departments.

D. Ward

Papers for publication and all editorial communications should be addressed to:
Professor G. Smith,
Editor, British Journal of Anaesthesia,
University Department of Anaesthesia,
Leicester Royal Infirmary,
Leicester LE1 5WW.
Telephone: 0533 470141
Fax: 0533 854487

All **business communications** should be sent to the Publishers: Professional & Scientific Publications Ltd, BMA House, Tavistock Square, London WC1H 9JR.

The GUIDE TO CONTRIBUTORS may be found in the advertisement section of this issue (pages ii, iv & vi).
Published monthly. Annual subscriptions: Worldwide £125.00; USA only $198.00 (direct orders only). Trainee rate: Worldwide £69.00. Airmail rates on application. ISSN 0007–0912. Orders must be accompanied by payment; cheques should be made payable to Professional and Scientific Publications. Orders and payments should be sent to Professional and Scientific Publications, BMA House, Tavistock Square, London WC1H 9JR. Orders in the United States of America may be sent to Professional and Scientific Publications, Box 560B, Kennebunkport, Maine 04046.

Group Advertisement Director, Mr R. Hayzen.
Advertisement Manager, Mr A. Allsop.
Publishing Manager, Mr D. Shaw.
BMA House, Tavistock Square, London WC1H 9JR. 071-387 4499.

Whilst every effort is made by the publishers and editorial committee to see that no inaccurate or misleading data, opinions or statement appear in this Journal, they wish to make it clear that the data and opinions appearing in the articles and advertisements herein are the responsibility of the contributor or advertiser concerned. Accordingly, the publishers and the editorial committee and their respective employees, officers and agents accept no liability whatsoever for the consequences of any such inaccurate or misleading data, opinions or statements. Whilst every effort is made to ensure that drug doses and other quantities are presented accurately, readers are advised that new methods and techniques involving drug usage, and described within this Journal, should only be followed in conjunction with the drug manufacturer's own published literature.

© Copyright: 1993 *British Journal of Anaesthesia*
All rights reserved. No part of this publication may be reproduced, stored in a retrieval system, or transmitted in any form by any means, electronic, mechanical, photocopying, recording or otherwise, without the prior permission of the *British Journal of Anaesthesia*, requests for which should be addressed to the **Editor**.

Published by Professional and Scientific Publications.
Printed in Great Britain by the University Press, Cambridge.

"I would have everie man write what he knowes and no more."—MONTAIGNE

BRITISH JOURNAL OF ANAESTHESIA

VOLUME 70, No. 6 JUNE 1993

EDITORIAL

IVOX

IVOX (Cardiopulmonics, Salt Lake City) is the registered acronym for an i.v. oxygenator. The device is undergoing Phase II evaluation of efficacy as part of the management of acute respiratory failure (ARF) in designated centres in Europe and the U.S.A. IVOX acts as a "lung assist" using hollow fibres for intracorporeal gas exchange and is designed to lie freely within the lumen of the superior and inferior venae cavae.

The drive to develop IVOX has been stimulated by the progressive limitation of the lungs to effect gas exchange in some cases of advanced lung injury and adult respiratory distress syndrome (ARDS). Mechanical, positive pressure or high frequency ventilation techniques are the mainstays of ventilatory support in acute respiratory failure. The pathophysiology of advanced lung injuries with increased microvascular permeability and disruption of alveolar architecture leads to a loss of area for gas exchange. In addition, there is evidence that large tidal volumes and positive pressure applied to the airways contribute to this pathology by increasing alveolar oedema and capillary rupture [1, 2].

The initial search for alternative methods of gas exchange led to the development of extracorporeal membrane oxygenation devices (ECMO). However, with these devices it is necessary to use large extracorporeal blood flows and full systemic anticoagulation. In addition, ECMO requires the continuous presence of perfusionist expertise and the technique is therefore limited to specialist referral centres and for short periods of operation only. More recently, however, advances in the technology of hollow fibres and gas exchange membranes have made artificial intracorporeal oxygen transfer feasible. Mortensen [3] developed these techniques and commenced clinical studies of the safety of IVOX in 1989. These early investigations showed no IVOX-related complications in 20 patients.

Ideally, such a device should comprise a hollow fibre oxygenator, capable of being inserted through a small peripheral venotomy so as to contribute significantly to gas exchange in the venous system. It should not induce thromboembolism or intimal damage and not necessitate full systemic anticoagulation. In addition, it should not impair caval blood flow. Most of these criteria are met by the IVOX device currently available.

The basic functional component is the hollow fibre. Each fibre is a polypropylene former, 35–45 cm in length, depending on the size selected; sizes range from French-gauge 7 to French-gauge 10, related to the transverse diameter in millimetres when the device is furled. An IVOX houses around 1000 of these fibres, each with an internal diameter of 190 μm and a wall thickness of 35 μm. Gas exchange occurs across the 1-μm outer layer around each fibre. This consists of cross-linked dimethyl siloxane overlying the numerous 0.3-μm diameter pores in the hollow fibre. The membrane is selectively permeable to gases, but not to liquids. Each fibre is crimped to encourage turbulent flow and further improve gas exchange. Resistance to thrombosis is produced using covalently bonded heparin and a proprietary thromboresistant outer layer. The fibres provide a total gas exchange area of between 0.21 m^2 and 0.52 m^2 for sizes French-gauge 7–10. However, this represents less than 10% of the equivalent gas exchange area in an ECMO circuit. In the adult, the area of lung surface for gas exchange is of the order of 75 m^2. Oxygen 100% is introduced through the central conduit of a coaxial gas transport tube, entering the fibres at their distal end. Carbon dioxide exchange and oxygen transfer occur as the gases are drawn back along the length of the fibres under a subatmospheric pressure of 300 mm Hg. Waste gases and water vapour are removed via the outer lumen. The negative pressure prevents gas embolization in the event of a fibre fracturing.

The IVOX is inserted as a tightly furled bundle to minimize the size of venotomy required and; it then expands to fill the inferior vena cava (IVC) and part of the superior vena cava. In the current clinical study, 89% of devices have been inserted via the right common femoral and 11% via the right internal jugular veins [personal communication, Cardiopulmonics]. It is important that the largest possible device is used. This has been emphasized by High and colleagues [4] and so it is recommended that the vein is assessed by ultrasound before insertion of the device. An obturator with a haemostatic valve and J-tipped guidewire are introduced and the position checked with an image intensifier. The device is advanced to occupy the entire length of the inferior and superior venae cavae and it is then unfurled to lie loosely within the venous lumen. The widest diameter of the device lies at the level of the intrahepatic IVC. The venotomy is repaired, a bacterial filter is connected to the oxygen inlet and a water trap inserted in the outlet tubing to protect the flow controller. The dose of heparin administered should produce an activated clotting time of no more than 250 s or partial thromboplastin time of 80–90 s. Systemic antibiotic prophylaxis is prudent.

The role of a pulmonary artery catheter (PAC) *in situ*, with the potential difficulties of entanglement, has yet to be fully evaluated. The principal advantage of using a PAC in the presence of an IVOX is that changes in pulmonary blood saturation can give an indication of oxygen delivery when taken in conjunction with cardiac output and haemoglobin. Gas transfer has been measured more accurately using an oxygen–helium mixture and the Haldane correction principle for the input and output gas phases [4]. Carbon dioxide elimination is measured easily using a capnograph and the volume of flow from the vacuum source.

The efficiency of IVOX in terms of gas exchange has been found to vary widely *in vitro*, in animals and in critically ill patients. It is apparent that IVOX can perform only as a lung *assist* device because its oxygen transfer capability is considerably less than basal requirements. The greater rates described are of the order of 140 ml min^{-1} [5], with comparable carbon dioxide removal.

The factors limiting gas transfer may not all be related to the constraints of hollow fibre membrane technology. Because 80 % of the IVOX length is positioned in the inferior vena cava, gas exchange is influenced by splanchnic flow. This may be decreased in ARDS, thereby reducing the efficiency of oxygenation [5]. There are patients whose gas exchange requirements cannot be assisted with IVOX, particularly if they have narrow veins, and it has been suggested [4] that the inability to use a French-gauge 9 or 10 device is a contraindication to IVOX therapy, as gas transfer is always inadequate. Although it is vital to insert the largest possible device, there is a risk of impeding the caval lumen, diverting venous return to the azygos and collateral systems and bypassing the oxygenator.

It has been suggested therefore, that the role of IVOX is to assist gas transfer in patients receiving maximal mechanical ventilation and who have shunt fractions less than 35 % [5]. ECMO would be an option for greater respiratory requirements. Other applications include the support of any potentially reversible ARF and to protect suture lines and minimize air leaks. It is predictable that it will be used for respiratory support before lung transplantation and for some patients requiring ventilatory support. Absolute contraindications are the inability to use anticoagulants safely, persistence of a low cardiac output or identification of bacteraemia or thrombus in the peripheral veins.

The future role of IVOX depends on hollow fibre membrane development and on refinements of technique such as placement of devices to improve oxygenation in mixed venous blood in the superior cava and even the pulmonary artery itself.

The outcome of current multicentre trials is awaited with interest. There will inevitably be problems in matching controls as in ECMO studies. However, the preliminary data (150 implants to date) suggest that the technique requires little more expertise than, for example, continuous flow renal support. It has the advantage of a longer duration of operation than ECMO: the mean duration of use in the current studies is 5.2 days, with a maximum of 29 days [personal communication]. Outcome data are not available yet, but preliminary results suggest early improvements in gas exchange and a reduction in the intensity of ventilator support. The technique may prove to be useful in maintaining life whilst lung injuries resolve, by helping to limit any detrimental effects of long-term mechanical ventilation.

J. Skoyles and M. Pepperman
Leicester

REFERENCES

1. Dreyfuss D, Soler P, Bassett G, Saumon G. High inflation pressure pulmonary edema; respective effects of high airway pressure, high tidal volume and positive end-expiratory pressure. *American Review of Respiratory Disease* 1988; 137: 1159–1164.
2. West JB, Tsukimoto K, Mathieu-Castello O, Prediletto R. Stress failure in pulmonary capillaries. *Journal of Applied Physiology* 1991; 70: 1731–1742.
3. Mortensen JD, Berry G. Conceptual and design features of a practical, clinically effective intravenous mechanical blood oxygen/carbon dioxide exchange device (IVOX). *International Journal of Artificial Organs* 1989; 12: 384–389.
4. High KM, Snider MT, Richard R, Russell GB, Stene JK, Campbell DB, Aufiero TX, Thieme GA. Clinical trials of an intravenous oxygenator in patients with adult respiratory distress syndrome. *Anesthesiology* 1992; 77: 856–863.
5. Kallis P, Al-Saady Naab M, Bennett D, Treasure T. Clinical use of intravascular oxygenation. *Lancet* 1991; 337: 549.

British Journal of Anaesthesia 1993; **70**: 605–611

ORIGINAL ARTICLES

COMPONENTS OF THE INSPIRATORY–ARTERIAL ISOFLURANE PARTIAL PRESSURE DIFFERENCE

M. J. LANDON, A. M. MATSON, B. D. ROYSTON, A. M. HEWLETT, D. C. WHITE AND J. F. NUNN

SUMMARY

We have measured the partial pressure of isoflurane simultaneously in inspired gas (PI_{iso}), end-expired gas (PE'_{iso}), mixed-expired gas ($P\bar{E}_{iso}$), arterial (Pa_{iso}) and mixed venous blood ($P\bar{v}_{iso}$) in six patients (aged 57–79 yr) anaesthetized with nitrous oxide, oxygen and isoflurane before surgery and after PE'_{iso} had been stable for at least 15 min. We related these changes to the various indices of pulmonary maldistribution to determine if they were sufficient to explain reported differences between PE'_{iso} and Pa_{iso}. Alveolar deadspace dilution of end-expired gas was calculated for carbon dioxide and this dilution factor used to calculate the "ideal" alveolar Piso (PA_{iso}) from the observed inspired and end-expired concentrations. Shunt fraction was measured for oxygen and then used to calculate the partial pressure of isoflurane in the pulmonary end-capillary blood (Pc'_{iso}) from the partial pressure in arterial and mixed venous blood. Mean (SE) values were: PI_{iso} 0.69 (0.05) kPa; PE'_{iso} 0.52 (0.04) kPa; PA_{iso} 0.50 (0.04) kPa; Pc'_{iso} 0.38 (0.04) kPa; Pa_{iso} 0.35 (0.03) kPa and $P\bar{v}_{iso}$ 0.22 (0.02) kPa; Pa_{iso}: PE'_{iso} 0.66 (0.02) kPa. The mean "ideal" alveolar to pulmonary end-capillary Piso difference was 0.12 (0.01) kPa and highly significant ($P < 0.001$). Pa_{iso} was substantially less than PE'_{iso} but, for isoflurane, the difference was reasonably constant (range 0.14–0.22 kPa). The difference was attributable in part to the effects of shunt and deadspace, but also a failure of equilibration of isoflurane between the alveolar gas and pulmonary end-capillary blood. It is likely to be different for other anaesthetics. We conclude that, while PE'_{iso} may adequately reflect Pa_{iso} for isoflurane, it cannot be assumed that the relation between end-expiratory gas and arterial partial pressures is the same for all anaesthetics. (Br. J. Anaesth. 1993; **70**: 605–611)

KEY WORDS

Anaesthetics, volatile: isoflurane. Pharmacokinetics: uptake.

The relation between the end-expired and arterial partial pressures of inhaled anaesthetic agents is important for both theoretical and practical reasons. In formulating the concept of MAC, the assumption is made that "the alveolar partial pressure is transmitted without change to the arterial blood" [1] and anaesthetic machines have been developed in which the administration of the agent is controlled by continuous measurement of the end-expired partial pressure [2]. Cromwell and colleagues [3], in a study on healthy volunteers breathing subanaesthetic concentrations of isoflurane, found no significant end-expiratory to arterial partial pressure difference. However, the recently published studies of Frei and colleagues [4] and Dwyer and colleagues [5] have shown an arterial to end-expiratory partial pressure ratio, after equilibration, ranging from 0.79 to 0.86. This ratio can be explained partly by the effects of venous admixture and alveolar deadspace, which are known to be increased in the anaesthetized patient. However, our own preliminary studies [unpublished] suggested that this explanation was insufficient to account for the whole of the arterial to end-expiratory partial pressure gradient for isoflurane. Eger [1] has suggested that anaesthetics of high molecular weight might fail to achieve uniform mixing within the alveolus, resulting in an "ideal" alveolar–pulmonary end-capillary partial pressure difference. To test this hypothesis, we have measured this difference for isoflurane in a group of patients in whom we simultaneously measured the shunt and physiological deadspace according to the three-compartment model (fig. 1). This enabled us to make an estimate of the likely effect of these factors on the end-expiratory–arterial partial pressure difference for isoflurane. In the course of these measurements, we have determined the mixed venous partial pressure of isoflurane, which has not been reported previously in man.

PATIENTS AND METHODS

With the approval of the Hospital Ethics Committee we studied six patients, aged between 57 and 79 yr, undergoing major elective vascular surgery, in whom placement of an arterial cannula and Swan–Ganz catheter was required for clinical reasons. Patients were premedicated and anaesthetized in a routine manner as dictated by the attending anaesthetist. Thiopentone 3–5 mg kg^{-1} was the induction agent

---

M. J. LANDON, PH.D.; B. D. ROYSTON, M.I.BIOL.; J. F. NUNN, M.D., PH.D., D.SC., F.R.C.ANAES.; Division of Anaesthesia, Clinical Research Centre, Harrow, Middx HA1 3UJ. A. M. MATSON, M.B., F.R.C.ANAES.; A. M. HEWLETT, M.B., F.R.C.ANAES.; D. C. WHITE, M.B., F.R.C.ANAES.; Department of Anaesthesia, Northwick Park Hospital, Harrow, Middx HA1 3UJ. Accepted for Publication: January 21, 1993.

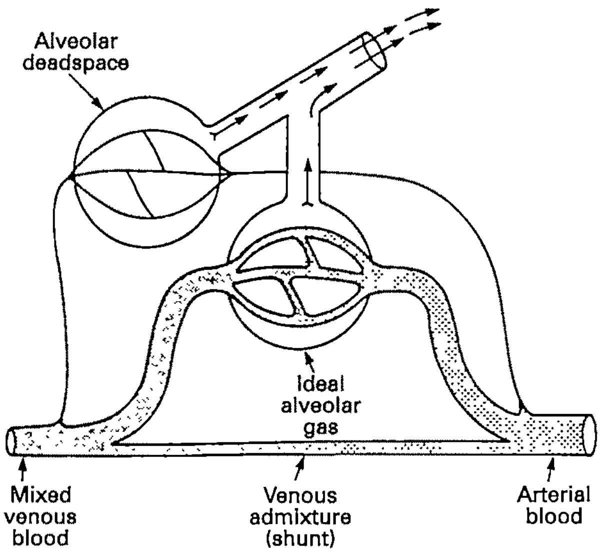


FIG. 1. Three-compartment model used as a basis for calculating ideal alveolar and pulmonary end-capillary partial pressures. (Reprinted with permission from [20].)

used in every case. Paralysis was with vecuronium 0.1 mg kg^{-1} or alcuronium 0.25–0.3 mg kg^{-1}. A cuffed tracheal tube was passed and a leak-proof seal obtained. Anaesthesia was maintained with nitrous oxide, 34–51 % oxygen and isoflurane. After induction, over-pressure of isoflurane (not greater than 2 %) was maintained for not more than 5 min after induction. The inspired concentration was then held constant (range 0.5–0.8 %) until blood samples had been taken (table I). Ventilation was with a Manley MP3 ventilator using a minute volume of approximately 6 litre.

Inspired oxygen percentage was measured continuously in the inspiratory limb of the circuit using a Servomex OA 580 paramagnetic analyser. Inspired and end-expired isoflurane percentages were monitored using a Datex Capnomac (95 % response time 900 ms) and end-expired carbon dioxide percentage was measured using an Ohmeda 5200 CO_2 monitor (95 % response time 360 ms). The sampling lines for isoflurane and carbon dioxide analysis were attached to the catheter mount of the tracheal tube, on the machine side of a Pall BB22–15 breathing system filter and the outputs recorded continuously on a Kipp and Zonen BD9 twin-channel chart recorder. The volume of the filter (approximately 90 ml) was included in the deadspace calculations.

Definitive measurements of end-expired carbon dioxide and inspired and end-expired isoflurane were taken from the chart recorder. A slow ventilatory frequency (approximately 12 b.p.m. with an inspired to expired ratio of 1:4) was deliberately set to allow a plateau for both inspired and expired gas to be recorded. The recorded end-tidal $P\mathrm{CO}_2$ bore the normal relation to the arterial $P\mathrm{CO}_2$ and the recorded inspired Piso agreed closely with a genuine upstream inspired sample measured by gas chromatography. Under these conditions, we are confident that we had a valid end-expiratory sample.

Arterial and mixed venous blood samples were taken after at least 25 min of anaesthesia at a constant inspired isoflurane percentage, with the end-expired isoflurane percentage changing by not more than 0.02 % for at least 15 min. Blood samples for arterial and mixed venous pH, $P\mathrm{O}_2$, $P\mathrm{CO}_2$ and oxygen saturation were obtained anaerobically in duplicate 2-ml, heparinized syringes, using three-way taps to clear the deadspace from both the arterial and pulmonary artery cannulae. Samples were stored on crushed ice for a maximum of 15 min before analysis using an IL 1302 blood-gas machine and an IL 282 Co-oximeter. Oxygen saturation of haemoglobin ($S\mathrm{O}_2$) was derived also from the virtual $P\mathrm{O}_2$ (calculated for 37 °C) using the Severinghaus nomogram [6]. In all cases the calculated saturation agreed with the measured saturation to within 2 % (corrected for carboxyhaemoglobin), the mean difference being 0.1 %. Separate 5-ml blood samples were also obtained to measure arterial and mixed venous haemoglobin concentration and PCV (Coulter Counter model S). Oxygen content of arterial, mixed venous and pulmonary capillary blood was then derived as:

$$[\mathrm{Hb}] \times S\mathrm{O}_2/100 \times 1.31 + 0.0225 \times P\mathrm{O}_2$$

where [Hb] = haemoglobin concentration corrected for carboxyhaemoglobin; $P\mathrm{O}_2$ was at 37 °C; 1.31 = haemoglobin combining factor obtained by Gregory [7]; 0.0225 = solubility coefficient of oxygen in whole blood. The pulmonary end-capillary $P\mathrm{O}_2$ was assumed to equal the alveolar $P\mathrm{O}_2$. This was derived from the Filley equation [8] which allows for nitrous oxide uptake.

Blood samples for measuring isoflurane partial pressure were obtained in gas-tight, heparinized, 2-ml all-glass syringes. Aliquots (0.5 ml) were then injected immediately through a Teflon seal into 2-ml glass vials with loosened screw caps; the caps were tightened immediately after injection. This procedure allowed the blood-gas mixture in the vial to remain at barometric pressure.

During the period of blood sampling, mixed expired gas was collected from the expiratory port of the patient ventilator into a Douglas bag for at least 3 min. After expired gas collection, two 20-ml and two 100-ml samples of inspired gas were obtained from the inspiratory limb of the patient ventilator, and two 20-ml and two 100-ml samples of mixed expired gas from the Douglas bag.

Barometric pressure, room temperature and the patient's tympanic membrane temperature (Mallinckrodt Mon-A-Therm) were noted at the time of sampling and the appropriate corrections made in calculations.

Mixed expired gas samples (100 ml) were analysed in duplicate for oxygen, carbon dioxide and isoflurane by the same monitors used for inspired and end-expired gas analysis. The 20-ml samples of inspired and mixed expired gas were analysed for isoflurane by gas chromatography to cross-check measurements taken from the chart recorder. The mean (SEM) difference was 0.011 (0.009) kPa. The mean value was calculated and used for subsequent calculations.

Isoflurane partial pressures in blood samples were measured as described by Knill and colleagues [9]

TABLE I. *Patient characteristics and ventilatory variables*

	Patient No.							
	1	2	3	4	5	6	Mean	SEM
Age (yr)/Sex	66 M	57 F	76 M	79 M	70 M	68 M	69	—
Weight (kg)	79.5	66.7	72.7	77.5	79.5	68.0	74.0	2.3
Time to sampling (min)	49	48	33	55	55	50	48	3
Inspired gas								
Oxygen (kPa)	32.8	45.4	33.5	48.8	30.6	30.2	36.9	3.3
Isoflurane (kPa)	0.76	0.82	0.50	0.64	0.60	0.81	0.69	0.05
End-expired gas								
Carbon dioxide (kPa)	4.3	3.8	5.4	3.2	4.9	4.6	4.4	0.3
Isoflurane (kPa)	0.61	0.60	0.35	0.52	0.42	0.63	0.52	0.04
Mixed-expired gas								
Oxygen (kPa)	30.5	38.3	31.1	46.9	28.6	28.3	34.0	3.0
Carbon dioxide (kPa)	2.7	1.7	2.4	2.1	2.5	2.2	2.3	0.1
Isoflurane (kPa)	0.62	0.66	0.44	0.56	0.47	0.65	0.57	0.04
Arterial blood								
Oxygen (kPa)	10.1	12.0	22.5	25.0	13.7	12.9	16.0	2.5
Oxygen saturation (%)	94.8	93.2	98.0	97.2	99.0	98.7	96.8	1.0
Haemoglobin (g dl^{-1})	16.8	13.1	14.3	10.8	10.2	12.7	13.0	1.0
Carbon dioxide (kPa)	4.5	4.1	5.6	4.2	5.6	5.6	4.9	0.3
pH	7.42	7.39	7.34	7.47	7.41	7.41	7.41	0.02
Isoflurane (kPa)	0.42	0.38	0.21	0.37	0.28	0.42	0.35	0.03
Mixed venous blood								
Oxygen (kPa)	4.4	8.1	6.6	4.7	5.1	4.7	5.6	0.6
Oxygen saturation (%)	67.3	85.0	82.4	69.9	76.5	75.3	76.1	2.8
Haemoglobin (g dl^{-1})	16.6	13.0	13.7	10.5	10.4	12.8	12.8	0.9
Carbon dioxide (kPa)	5.2	4.7	5.9	4.8	6.1	6.3	5.5	0.3
pH	7.38	7.37	7.32	7.43	7.38	7.38	7.38	0.01
Isoflurane (kPa)	0.23	0.20	0.17	0.22	0.21	0.30	0.22	0.02
Calculated values								
Alveolar deadspace dilution factor	4.44	7.32	3.57	23.81	12.50	17.86	11.58	3.39
Ideal alveolar isoflurane (kPa)	0.60	0.58	0.34	0.48	0.39	0.59	0.50	0.04
Shunt (%)	13.72	37.23	3.53	10.20	13.85	10.25	14.80	4.74
Pulmonary end-capillary isoflurane (kPa)	0.45	0.49	0.21	0.39	0.29	0.43	0.38	0.04
Isoflurane ratios								
End-expired: inspired	0.80	0.73	0.70	0.81	0.70	0.78	0.75	0.02
Arterial: inspired	0.55	0.46	0.42	0.58	0.47	0.52	0.50	0.02
Mixed venous: arterial	0.55	0.53	0.81	0.59	0.75	0.71	0.66	0.05
Arterial: end-expired	0.69	0.63	0.60	0.71	0.67	0.67	0.66	0.02
Ideal alveolar: end-expired	0.98	0.97	1.00	0.94	0.93	0.95	0.96	0.01
Arterial: Pulm. end-cap.	0.93	0.79	1.00	0.95	0.93	0.98	0.93	0.03
Pulm. end-cap.: end-expired	0.74	0.80	0.60	0.75	0.71	0.68	0.71	0.03
Isoflurane differences								
Mixed venous–arterial (kPa)	0.19	0.18	0.04	0.15	0.07	0.12	0.12	0.02
End expired–arterial (kPa)	0.19	0.22	0.14	0.15	0.14	0.21	0.18	0.02
Residual gradient								
Ideal alveolar minus pulmonary end-capillary (kPa)	0.15	0.09	0.13	0.09	0.10	0.16	0.12	0.01

using a Pye 104 gas chromatograph (GC) fitted with a 60-µl or 500-µl gas sampling loop and a flame ionization detector. The carrier gas was oxygen-free nitrogen. Oven temperature was 125 °C and detector temperature was 175 °C. The blood-gas samples were equilibrated at 37 °C in a thermostatically controlled chamber by gentle rotation in a vertical plane at 20 r.p.m. for 45 min. A portion of the gas was then flushed into the gas sampling loop of the GC to obtain an isoflurane partial pressure and the remaining gas expelled. The same volume of unequilibrated humidified air was added to the vial and allowed to equilibrate as before. The procedure was repeated four times in total. The natural logarithms of the chromatogram peak heights from each of the four equilibrated gas phases were plotted against the serial number of the equilibration. Assuming that the partition coefficient of isoflurane is independent of absolute tension, these plots should fall on a straight line. The *Y*-intercept is proportional to the partial pressure of isoflurane in the original blood sample. Regression lines for each pair of samples were obtained using the least squares technique and the results averaged. The mean correlation coefficient for the series was −0.9958 (0.0025) and the coefficient of variation between duplicate samples was 2.1%.

To check the accuracy of our isoflurane measurements, 26 normal blood samples were tonometered in a gas flow of known isoflurane partial pressures

(Piso). The partial pressure in the samples was determined as described above. The mean (SE) Piso in the gas phase was 0.241 (0.008) kPa and that in the blood samples 0.243 (0.008) kPa. The difference between paired analyses was not significant (t = 0.76).

Analytical equipment was calibrated before and after each study. The GC was calibrated using the same standard gas mixtures as those used for calibration of the Capnomac and the Ohmeda CO_2 monitor was calibrated against the same standard as that used for blood-gas analysis. The Servomex OA 580 was calibrated with oxygen-free nitrogen and room air. The Datex Capnomac, the Ohmeda CO_2 monitor, the Servomex paramagnetic analyser and GC were all checked for linearity before the study.

CALCULATIONS (fig. 1)

Dilution factor for end-expiratory gas

The inspired partial pressure of isoflurane, $P\text{I}_{\text{iso}}$, was calculated as follows:

$$P\text{I}_{\text{iso}} = F\text{I}_{\text{iso}}(P\text{B} - P\text{H}_2\text{O})$$

where $F\text{I}_{\text{iso}}$ = fractional inspired concentration of isoflurane in dry gas; $P\text{B}$ = barometric pressure; $P\text{H}_2\text{O}$ = saturated vapour pressure of water at body temperature.

On the assumption that the alveolar deadspace gas has the same composition as inspired gas, the dilution factor for end-expiratory gas by alveolar deadspace gas is:

$$\frac{P\text{A}_{\text{CO}_2} - P\text{E}'_{\text{CO}_2}}{P\text{A}_{\text{CO}_2} - P\text{I}_{\text{CO}_2}} \qquad (1)$$

where $P\text{A}_{\text{CO}_2}$ = alveolar $P\text{CO}_2$; $P\text{E}'_{\text{CO}_2}$ = end-expired $P\text{CO}_2$; $P\text{I}_{\text{CO}_2}$ = inspired $P\text{CO}_2$.

On the assumptions that $Pa_{\text{CO}_2} = P\text{A}_{\text{CO}_2}$ and $P\text{I}_{\text{CO}_2} = 0$, then:

$$\text{dilution factor (dil)} = \frac{Pa_{\text{CO}_2} - P\text{E}'_{\text{CO}_2}}{Pa_{\text{CO}_2}} \qquad (2)$$

where Pa_{CO_2} = arterial $P\text{CO}_2$.

Equation (1) was then applied to isoflurane and the ideal alveolar partial pressure of isoflurane was then derived as:

$$P\text{A}_{\text{iso}} = \frac{P\text{E}'_{\text{iso}} - (\text{dil} \times P\text{I}_{\text{iso}})}{1 - \text{dil}}$$

where $P\text{A}_{\text{iso}}$ = alveolar Piso; $P\text{E}'_{\text{iso}}$ = end-expiratory Piso; $P\text{I}_{\text{iso}}$ = inspired Piso.

Dilution factor for arterial blood

The shunt fraction was calculated using the classical shunt equation, deriving arterial and mixed venous oxygen content from $S\text{O}_2$, $P\text{O}_2$ and haemoglobin concentration as described above:

$$\text{Shunt fraction} = \frac{Cc'_{\text{O}_2} - Ca_{\text{O}_2}}{Cc'_{\text{O}_2} - C\bar{v}_{\text{O}_2}}$$

where Cc'_{O_2} = pulmonary end-capillary blood oxygen content; Ca_{O_2} = arterial blood oxygen content and $C\bar{v}_{\text{O}_2}$ = mixed venous blood oxygen content. The shunt equation was applied to isoflurane and the pulmonary end-capillary partial pressure of isoflurane (Pc'_{iso}) derived as:

$$Pc'_{\text{iso}} = \frac{Pa_{\text{iso}} - (\text{shunt} \times P\bar{v}_{\text{iso}})}{1 - \text{shunt}}$$

where Pa_{iso} = arterial Piso; $P\bar{v}_{\text{iso}}$ = mixed venous Piso.

The data are shown as mean (SE) and where appropriate the difference between means was tested using Student's t test.

RESULTS

After 25 min with a constant inspired isoflurane concentration, a relatively steady state was achieved with the end-expired isoflurane concentration changing by less than 0.02% during the last 15 min of this period, and by less than 0.01% during the 5-min period of measurements. Inspired Piso was 0.69 (0.05) kPa and end-expiratory Piso was 0.52 (0.04) kPa, giving an end-expired: inspired ratio of 0.75 (0.02). Arterial Piso was 0.35 (0.03) kPa, with an arterial: end-expired ratio of 0.66 (0.02). Piso of the mixed venous blood was 0.22 (0.03) kPa (table I).

At the time of the isoflurane measurements, the physiological deadspace (including apparatus deadspace) was 53.6 (3.1)%, and the arterial–end-expiratory $P\text{CO}_2$ difference 0.56 (0.16) kPa. Calculated for carbon dioxide, the dilution factor for alveolar gas by alveolar deadspace was 11.58 (3.39)%. The shunt fraction was 14.8 (4.74)%, with an ideal alveolar to arterial $P\text{O}_2$ gradient of 14.2 (2.21) kPa.

Derived values

Applying the alveolar deadspace dilution factor to isoflurane, the calculated ideal alveolar Piso would be 0.50 (0.04) kPa; this was 96 (1.0)% of the end-expired value, a difference between the two of only 0.02 kPa.

Applying the shunt fraction to isoflurane, the pulmonary end-capillary Piso would be 0.38 (0.04) kPa which is only 0.03 kPa greater than the arterial Piso. The residual, unexplained, difference between ideal alveolar Piso and pulmonary end-capillary Piso was 0.12 (0.01) kPa. The difference from zero for this gradient was highly significant ($P < 0.001$) (fig. 2).

DISCUSSION

The presence of an end-expiratory to arterial anaesthetic partial pressure difference has been demonstrated for several volatile anaesthetic agents in healthy subjects. Our mean measured arterial: end-expired Piso ratio for isoflurane was 0.66 (0.02), which is less than the values obtained by Frei and colleagues [4] and Dwyer and colleagues [5], but we are in full agreement that a substantial difference exists. This gradient has been attributed hitherto to the increased alveolar deadspace and venous admixture (shunt) found in anaesthetized patients [10–14].

In the present study, the values for physiological

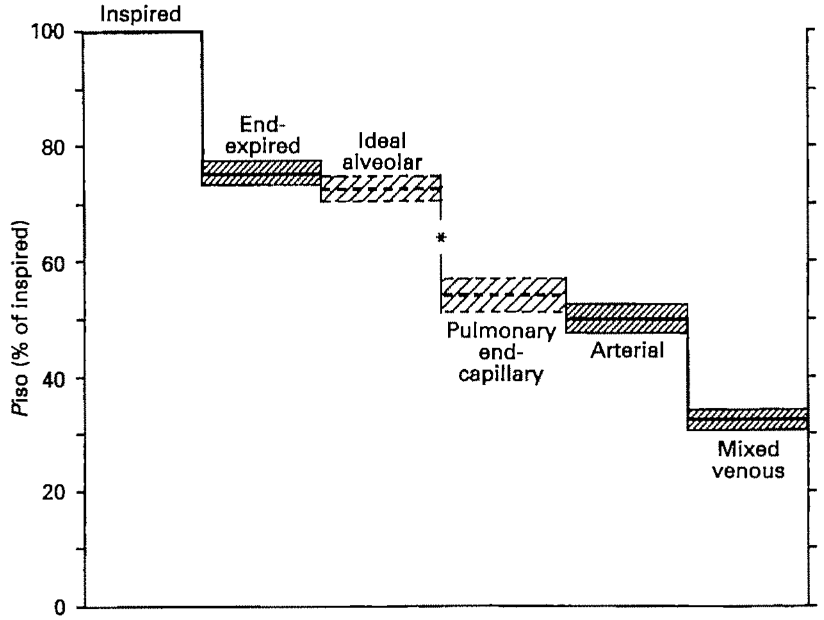


FIG. 2. Cascade of isoflurane partial pressures (*P*iso) from inspired gas to mixed venous return expressed as a percentage of inspired partial pressure. Solid lines and close hatching show measured values (mean, SEM). Dashed lines and wide hatching show *calculated* values (mean, SEM). *Highlights the unexplained difference between ideal alveolar and pulmonary end-capillary partial pressures.

deadspace and the arterial–end-expiratory $P\text{CO}_2$ difference were typical for anaesthetized patients with tracheal tube and apparatus deadspace included [15]. The alveolar deadspace dilution factor of 11.6 % can have little effect on the ideal alveolar–end-expiratory difference, partly because it is normally quite small during anaesthesia and partly because the alveolar deadspace gas would contain isoflurane approximating in composition to the inspired gas. Thus the ideal alveolar *P*iso is very little less than the measured end-expired value: only 0.02 kPa in the present study. Similar considerations would apply to ventilation of alveolar units of large (but not infinite) ventilation: perfusion ratio simulating a true alvolar deadspace.

The mean shunt in this study accords very closely with previous observations on anaesthetized patients in the age range 57–79 yr [12]. If the three-compartment model is applied to isoflurane, the pulmonary end-capillary *P*iso would be only 0.03 kPa greater than the arterial *P*iso. This is to be expected because, in common with carbon dioxide, *P*iso bears a constant relation to content and the partial pressures in mixed venous and arterial blood are not greatly different. It is only because of its alinear dissociation curve that oxygen has so large an alveolar–arterial $P\text{O}_2$ difference in the presence of a shunt. Thus the corrections for shunt and deadspace together account for only 33 % of the total end-expired to arterial *P*iso difference (fig. 2, table I).

Our analysis has followed the classical three-compartment model of the lung suggested by Riley and Cournand [16]. Although this approach treats relative maldistribution of ventilation and perfusion as though it contributed to alveolar deadspace and shunt, it gives values for these parameters which permit satisfactory prediction of arterial $P\text{CO}_2$ and $P\text{O}_2$ in a wide range of clinical situations. In this analysis some approximations are made, and it remains to consider how these effect the validity of our conclusions.

The Riley analysis assumes that the alveolar deadspace gas contains gas which has the same composition as inspired gas. In fact, a small quantity of end-expiratory gas from the anatomical deadspace must be re-inhaled into the alveolar deadspace. If, as seems likely, this effect were to increase the $P\text{CO}_2$ of the alveolar deadspace gas by 0.4 kPa, then the mean value for the alveolar deadspace dilution factor would be increased by about 0.9 % (equation (1)). This would result in a reduction in the calculated ideal alveolar *P*iso of about 0.002 kPa (equation (2)). However, the Riley analysis also assumes that ideal alveolar $P\text{CO}_2$ equals arterial $P\text{CO}_2$. This is not so when there is an appreciable shunt, but the effect is usually very small because the mixed venous–arterial $P\text{CO}_2$ difference is normally only about 10 % of the arterial–mixed venous $P\text{O}_2$ difference, and much less when the concentration of oxygen in the inspired gas is increased. A mean shunt of 14.8 %, with our measured values for mean arterial and mixed venous $P\text{CO}_2$, would reduce the mean ideal alveolar $P\text{CO}_2$ from an assumed 4.9 kPa to 4.8 kPa. Substitution of the corrected value into equation (1) reduces the mean alveolar deadspace dilution factor by about 2 %, increasing the calculated ideal alveolar *P*iso by about 0.004 kPa. This offsets the previous correction and the net result is a very small *increase* (0.002 kPa) in the calculated ideal alveolar *P*iso.

Calculation of shunt in the Riley analysis depends on the value for ideal alveolar $P\text{O}_2$, which is derived from the ideal alveolar $P\text{CO}_2$, conventionally assumed to be equal to the arterial $P\text{CO}_2$. Applying the correction to the alveolar $P\text{CO}_2$ derived in the previous paragraph, the calculated shunt would be decreased by less than 0.1 %. This would increase the derived pulmonary end-capillary *P*iso by a negligible quantity—less than 0.0002 kPa. This would have no significant effect on the residual gradient.

Anaesthesia results in compression atelectasis of dependent lung zones, with a true shunt which relates to the amount of atelectasis observed by computed tomography [17]. However, during anaesthesia about 50% of the observed alveolar to arterial $P\text{CO}_2$ difference and the venous admixture (calculated from the shunt equation) is explained by an increased spread of ventilation:perfusion ratios and, in particular, as a result of perfusing alveolar units with ventilation:perfusion ratios in the range 0.005–0.1 [11, 12, 18]. This has a much greater effect on $P\text{O}_2$ than on either $P\text{CO}_2$ or *P*iso because of the upward convexity of the oxyhaemoglobin dissociation curve. However, this factor is considered in calculating the equivalent "shunt effect" of perfusion in areas of low ventilation:perfusion ratios.

Dueck and colleagues [19] have argued that the method of analysing $V\text{A}/Q$ relations in the lungs used by Nunn, Bergman and Coleman [12] and in our present study has limitations because calculated shunt increases with smaller inspired oxygen concentration. However, the range of fractional inspired concentrations of oxygen used in our study was 0.34–0.50 and it is likely that most of the calculated venous admixture represents true shunt. Even if our calculations of shunt are underestimates, a large shunt, in the region of 50%, would be required to explain the observed end-expired–arterial *P*iso difference. In spite of the limitations of the three-compartment model, it seems improbable that abnormal distribution of ventilation:perfusion ratios, sufficient to cause the observed alveolar–arterial $P\text{O}_2$ difference, could explain more than a small fraction of the observed end-expiratory–arterial *P*iso difference.

If there is indeed a finite ideal alveolar–pulmonary end-capillary *P*iso difference, there are two possible explanations: there could be resistance to transfer through the alveolar capillary membrane; or isoflurane may not achieve uniform distribution throughout the alveoli during the ventilatory cycle. It is difficult to say how the physical properties of isoflurane could influence its ease of passage through the alveolar–capillary membrane. There is no measurable impairment of oxygen or carbon dioxide, except under conditions of maximal exercise at decreased inspired $P\text{O}_2$. For isoflurane, both water and lipid solubilities are greater than those of oxygen, which should favour its passage through the membrane. However, its molecular weight is much greater.

Gas mixing within the alveoli occurs predominantly by diffusion and the rate at which a gas diffuses is inversely proportional to the square root of its molecular weight. Under normal circumstances, incomplete mixing of gases such as oxygen and carbon dioxide is unlikely to occur. The average diameter of the human alveolus at functional residual capacity is about 200 µm and it is likely that mixing of gases of low molecular weight is almost instantaneous over the very small distance from the centre to the periphery [20]. However, this may not be the case for isoflurane or other anaesthetics of relatively high molecular weight. Georg and colleagues [21] studied diffusion differences in the gas phase of the lungs of normal and emphysematous subjects using three inert gases of widely different molecular weights and found that the ratio of heavier to lighter gas varied with the volume of expired gas. These differences were exaggerated in emphysematous subjects. Further evidence that the changes in ratio are the result of differing rates of gas diffusion comes from breath-holding experiments: when a breath is held for 30 s the ratios in the expired gas are independent of the volume expired [22]. Robertson, Whitehead and Hlastala [23] observed a difference in the retention of isoflurane (184.5 Da) and acetylene (26 Da) during its passage from blood to expired air. This could not be explained by differences in partition coefficients, and they concluded that it was consistent with a diffusion-related impairment of gas exchange. In support of this view, they cited several authors who had reported differences in anatomical deadspace as measured with gases of markedly different molecular weight.

This evidence suggests that some volatile anaesthetics may not be uniformly distributed throughout the alveolus and these inhomogeneities may make some contribution to the gradient between ideal alveolar gas and pulmonary end-capillary blood. It is likely that this gradient will differ for different anaesthetics. For nitrous oxide, Eger and colleagues [24] found a $Pa{:}P\text{E}'$ ratio of 0.98 after 8 min, implying that when deadspace and shunt have been accounted for, there is no residual gradient.

Our results and those of Frei and colleagues [4] and Dwyer and colleagues [5] show clearly that end-expiratory partial pressures of some volatile anaesthetics are greater than those in arterial blood, and must be greater than at the site of action in the brain. Thus MAC is related to values which differ significantly from those at the site of action. Nevertheless, it is not possible to measure partial pressures at the site of action, nor is it feasible to monitor arterial partial pressure in the present state of technology. It is therefore fortunate that the arterial:end-expiratory *P*iso ratio was found to be remarkably constant at 0.66 (0.02). Thus measuring end-expiratory partial pressures in relation to MAC values is a valid method to monitor the depth of anaesthesia. However, comparison of MAC values as an absolute measure of potency might be questioned if the arterial:end-expired ratios are significantly different, as seems to be the case at least for nitrous oxide and isoflurane.

To our knowledge, mixed venous concentrations of an anaesthetic have not been measured before in humans and on average they were 40% smaller than the arterial value. However, it can be predicted that, in humans, it would take several days of anaesthesia for the mixed venous concentration of isoflurane to equal that of arterial blood, when the inspired–end-expiratory–arterial gradient would disappear. The presence of this gradient for isoflurane is therefore likely to persist even during prolonged anaesthesia.

In conclusion, we suggest that the effects of shunt and deadspace are small and the main reason for the end-expired to arterial partial pressure gradient for isoflurane observed by Frei and colleagues [4], Dwyer and colleagues [5] and ourselves may be the failure to achieve uniform distribution within the alveolus. This will impede changes in anaesthetic partial pressure in blood and therefore tissues, thus hindering the attainment and reversal of the anaesthetic state. Further studies on other volatile anaesthetics are needed.

REFERENCES

1. Eger EI. *Anaesthetic Uptake and Action*. Baltimore, Maryland: The Williams & Wilkins Company, 1974.
2. Ross JAS, Wloch RT, White DC, Hawes DW. Servo-controlled closed circuit anaesthesia—a method for automatic control of anaesthesia by a volatile agent in oxygen. *British Journal of Anaesthesia* 1983; **55**: 1053–1060.
3. Cromwell TH, Eger EI, Stevens WC, Dolan WM. Forane uptake, excretion and blood solubility in man. *Anesthesiology* 1971; **35**: 401–408.
4. Frei FJ, Zbinden DA, Thompson DA, Reider HU. Is the end-tidal partial pressure of isoflurane a good predictor of its arterial partial pressure? *British Journal of Anaesthesia* 1991; **66**: 331–339.
5. Dwyer RC, Fee JPH, Howard PJ, Clarke RSJ. Arterial washin of halothane and isoflurane in young and elderly adult patients. *British Journal of Anaesthesia* 1991; **66**: 572–579.
6. Roughton FJW, Severinghaus JW. Accurate determination of O_2 dissociation curve of human blood above 98.7% saturation with data on O_2 solubility in unmodified human blood from 0 degrees to 37 degrees C. *Journal of Applied Physiology* 1973; **35**: 861–869.
7. Gregory IC, Hulands GH, Millar RA. The *in vivo* oxygen capacity of haemoglobin in man. *Journal of Physiology (London)* 1971; **219**: 31P.
8. Filley GF, MacIntosh DJ, Wright GW. Carbon monoxide uptake and pulmonary diffusing capacity in normal subjects at rest and during exercise. *Journal of Clinical Investigation* 1954; **33**: 530–539.
9. Knill RL, Lok PYK, Strupat JP, Lam AM. Blood solubility of isoflurane measured by a multiple gas phase equilibration technique. *Canadian Anaesthetists Society Journal* 1983; **30**: 155–161.
10. Bendixen HH, Hedley-Whyte J, Laver MB. Impaired oxygenation in surgical patients during general anesthesia with controlled ventilation. *New England Journal of Medicine* 1963; **269**: 991–996.
11. Nunn JF. Factors influencing the arterial oxygen tension during halothane anaesthesia with spontaneous ventilation. *British Journal of Anaesthesia* 1964; **37**: 327–341.
12. Nunn JF, Bergman NA, Coleman AJ. Factors affecting the arterial oxygen tension during anaesthesia with artificial ventilation. *British Journal of Anaesthesia* 1965; **37**: 898–914.
13. Price HL, Cooperman LH, Warden JC, Morris JJ, Smith TC. Pulmonary hemodynamics during general anesthesia in man. *Anesthesiology* 1969; **30**: 629–636.
14. Hulands GH, Greene R, Iliff LD, Nunn JF. Influence of anaesthesia on the regional distribution of perfusion and ventilation in the lung. *Clinical Science* 1970; **38**: 451–460.
15. Kain ML, Panday J, Nunn JF. The effect of intubation on the deadspace during halothane anaesthesia. *British Journal of Anaesthesia* 1969; **41**: 94–102.
16. Riley RL, Cournand A. "Ideal" alveolar air and the analysis of ventilation/perfusion relationships in the lung. *Journal of Applied Physiology* 1949; **1**: 825–836.
17. Hedenstierna G. Gas exchange during anaesthesia. *British Journal of Anaesthesia* 1990; **41**: 94–102.
18. Gummerson L, Tokics L, Gustavsson H, Hedenstierna G. Influence of age on atelectasis formation and gas exchange impairment during general anaesthesia. *British Journal of Anaesthesia* 1991; **66**: 423–430.
19. Dueck R, Young I, Clausen J, Wagner PD. Altered distribution of pulmonary ventilation and blood flow following induction of inhalational anesthesia. *Anesthesiology* 1980; **52**: 113–125.
20. Nunn JF. *Applied Respiratory Physiology*, 3rd Edn. London: Butterworth & Co., 1987.
21. Georg J, Lassen NA, Mellemgard K, Vinther A. Diffusion in the gas phase of the lungs in normal and emphysematous subjects. *Clinical Science* 1965; **29**: 525–532.
22. Cummings G, Horsfield K, Jones JG, Muir CF. The influence of gaseous diffusion on the alveolar plateau at different gas volumes. *Respiration Physiology* 1967; **2**: 386–398.
23. Robertson HT, Whitehead J, Hlastala MP. Diffusion-related differences in elimination of inert gases from the lung. *Journal of Applied Physiology* 1986; **61**: 1162–1172.
24. Eger EI, Babad AA, Regan MJ, Larson CP, Shargel R, Severinghaus JW. Delayed approach of arterial to alveolar nitrous oxide partial pressures in dog and in man. *Anesthesiology* 1966; **27**: 288–297.

British Journal of Anaesthesia 1993; 70: 612–616

COMPARISON OF THE SEDATIVE AND AMNESIC EFFECTS OF MIDAZOLAM AND PROPOFOL

M. R. POLSTER, P. A. GRAY, G. O'SULLIVAN, R. A. McCARTHY AND G. R. PARK

SUMMARY

We have compared the sedative and amnesic effects of midazolam and propofol in 35 volunteers. Sedation was measured by simple reaction time immediately before and after a bolus injection and 1 h after the commencement of a subsequent continuous infusion. Memory was measured three times using two memory tests: perceptual facilitation provided an implicit memory measure and recognition provided an explicit memory measure. Propofol and midazolam had similar sedative effects both immediately after bolus doses and after 1-h continuous infusions of the drugs. In contrast, midazolam had a more profound amnesic effect than propofol on the recognition memory test. The drugs had little effect on performance with the implicit memory test. Performance on the memory tests was unrelated to sedation. (Br. J. Anaesth. 1993; **70**: 612–616)

KEY WORDS

Hypnotics, benzodiazepines: midazolam. Anaesthetics, intravenous: propofol. Memory: amnesia.

The amnesic effects of midazolam have been documented [1, 2], but there are only clinical observations to suggest that propofol might possess amnesic properties [3]. This study has compared these two drugs directly to establish their relative potency as amnesia producing agents.

Memory may be dependent partly on the subject's level of arousal or alertness at the time of learning. This makes it imperative to use an independent cognitive measure of sedation in order to eliminate the possibility that the amnesic effects are related to sedation. In this study, we have therefore used a simple reaction time test to measure and maintain the same level of sedation for the two agents.

Neuropsychological and cognitive analyses have indicated that memory should not be considered as a single entity [4–6]. A major distinction has been drawn between conventional memory tests such as recall and recognition ("explicit" memory tests), and tests that do not require the subject to recollect overtly the previous learning episode ("implicit" memory tests) [7]. For example, if subjects are asked to identify a degraded stimulus on two occasions, they often do so more easily on the second occasion, even if they do not remember the first presentation. Such an effect can be labelled perceptual facilitation, and is independent of recognition memory. In view of the evidence for this dissociation, we thought it was important to establish what type of memory was affected by propofol and midazolam.

One of three stages of the memory process—encoding, storage or retrieval—may be affected by the drugs. In order to isolate these stages of memory processing, it was necessary to determine if memory loss is a manifestation of the so-called state dependency phenomenon which is seen when subjects cannot recall material under a pharmacological condition that differs from the state at learning, but then recall the same information when the original learning condition is re-established.

Therefore we have compared the effects of propofol and midazolam on implicit and explicit memory under conditions in which sedation was matched by simple reaction time. The design was refined further to include analyses of state dependency and an evaluation of the stage of memory processing most affected by these drugs. Previous studies on benzodiazepines led us to expect a major effect of midazolam on explicit memory, but its effects on implicit memory remain undetermined [8, 9]. The literature also suggests that benzodiazepines in general (and therefore midazolam in particular) may act as a primary amnesogenic agent rather than as a "state dependent" influence [10].

SUBJECTS AND METHODS

We studied 35 healthy (ASA I) volunteers, aged 18–40 yr, in two sessions 1 week apart. They were allocated randomly to receive midazolam, propofol or placebo in each of two testing sessions. This created seven groups of five subjects necessary to test for state-dependent effects: placebo–placebo, placebo–propofol, placebo–midazolam, propofol–

M. R. POLSTER, B.PSYCH., PH.D., Department of Psychology, University of Arizona, Tucson, AZ 85721, U.S.A. P. A. GRAY, M.B., B.S., F.R.C.ANAES.; G. R. PARK, M.D., F.R.C.ANAES.; Department of Anaesthetics, Addenbrookes Hospital, Hills Road, Cambridge. G. O'SULLIVAN, M.B., B.S., F.F.A.R.A.C.S.; Department of Anaesthetics, St Mary's Hospital, Sydney, Australia. R. A. MCCARTHY, B.SC., PH.D., Department of Experimental Psychology and Kings College Research Centre, Cambridge University, Cambridge. Accepted for Publication: January 21, 1993.

Correspondence to G.R.P.

TABLE I. *Summary of test procedure on first day*

Test	Drug administration	Name
Reaction time 1 Word list 1	None	Pre-drug Pre-drug
	Bolus 1	
Reaction time 2		None
	Bolus 2 (if necessary)	
Reaction time 3		Peak effect
	Continual infusion	
Words list 2 Reaction time 4 Words list 3		Within drug One hour Seven days

placebo, propofol–propofol; midazolam–placebo; midazolam–midazolam. Ethics Committee approval was received, and written informed consent was obtained from each volunteer. There were no differences in age distribution for the seven groups.

Subjects were presented with a series of tests before and during administration of midazolam, propofol or placebo. Table I provides a summary of the procedure on the first day; the same procedure was used on the second day, except that there was no presentation before giving the drug. Undiluted propofol 10 mg ml^{-1}, midazolam 1 mg ml^{-1} diluted with 0.9% saline, or placebo (0.9% saline) was administered using a Grazeby syringe pump via an i.v. cannula in the non-dominant arm. Both the subject and the cognitive experimenter were blind to the solution being administered.

Sedative effect of propofol and midazolam

At each measurement of reaction time, subjects were presented with a block of 48 trials using an Apple Macintosh computer and the commercially available PsychLab program [11]. Each trial consisted of a warning signal (the word "READY") presented for 500 ms, followed by a variable foreperiod (a blank screen) for 500, 1000 or 1500 ms, followed by a target stimulus (the letter X). Within each block of 48 trials, there were 16 of each foreperiod interval, distributed randomly, but no interval occurred more than three times consecutively. Subjects used the dominant hand to press the space bar on the keyboard as soon as the X appeared. After an interval of 2.5 s, the next trial began with the presentation of the warning signal. Reaction time was recorded to the nearest millisecond.

Subjects were presented with one block immediately before any injections. Block two was presented immediately after the initial bolus dose of midazolam 0.04 mg kg^{-1}, propofol 0.07 mg kg^{-1} or placebo (0.9% saline), and was used only to determine if a second bolus dose would be administered. Block three was administered after a second bolus dose of midazolam, propofol or placebo if required and measured the peak sedative effects of the two drugs. Block four was administered 1 h later, during which time a continuous i.v. infusion was administered (midazolam 0.035 mg kg^{-1} h^{-1}; propofol 1.27 mg kg^{-1} h^{-1}). The initial infusion rates were midazolam 0.04 mg kg^{-1} h^{-1} and propofol 1.5 mg kg^{-1} h^{-1}. These doses were scaled down from data obtained by Wilson, Mackenzie and Grant [3], making allowances for the differences in age and ASA grade and were adjusted if subjects were unable to complete the simple reaction time task.

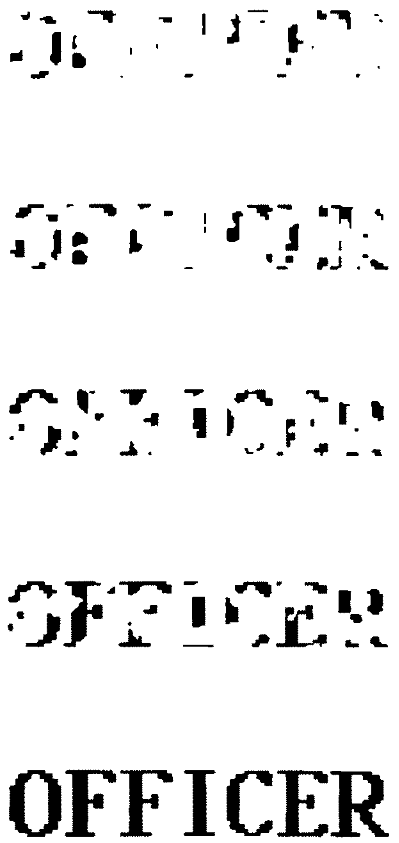


FIG. 1. Example of word fragmentation.

Amnesic effects of propofol and midazolam

Five sets of 20 words were created. Each word was presented at five levels of fragmentation ranging from one (very degraded) through to five (complete word) (fig. 1). Each version of the word was shown for up to 5 s, during which time the volunteer was asked to identify it. If it was not named the next less degraded version was shown. This procedure continued until the subject identified the word correctly. The subject's response to each version and the number of versions required to identify the word were recorded on the computer. The word lists were presented in a counterbalanced design, such that list one occurred equally often as a test item across subjects.

Each subject saw 20 fragmented words before being given propofol, midazolam or placebo on the first day of testing. Memory was tested for these items 1 h later during the continual infusion, by presenting the same words mixed with a second set of 20 words, which served as distractor items. This test served as a baseline measure of performance. Memory for the second stimulus set was tested approximately 1 h later, mixed with a third list of 20 words that served as distractors. This memory test measured the ability of subjects to encode new information under the influence of the drugs. Memory for the third set was tested 7 days later by presenting the same items mixed with another new set of 20 words which served as distractor items.

Two measures of memory were obtained in each test: perceptual facilitation on items presented twice, and recognition. Identifying the word in fewer versions on the second presentation is evidence for the effect (or memory) of the previous presentation, and is termed perceptual facilitation. Because it does not require conscious recollection, perceptual facilitation is considered an implicit memory test. Recognition memory was measured by having subjects respond Yes, Probably Yes, Probably No and No, and provided an index of explicit memory. The non-parametric sensitivity measure, *A*, was then calculated as a measure of recognition memory [12].

Unless otherwise stated, all the data were analysed using mixed analyses of variance and significance levels were set at $P < 0.05$.

RESULTS

Sedative effects of propofol and midazolam

Response times in the range 150–1000 ms were included in the analysis, thereby excluding trials on which the subject was extremely slow to respond and trials on which the stimulus was anticipated. Harmonic means were calculated for each subject's residual data points [13]. Figure 2 shows that there was no difference in response time performance across the three groups of subjects before the drugs were given ($P > 0.05$). Immediately after the drug was given, the midazolam and propofol groups had significantly increased reaction times compared with placebo ($P < 0.001$), but the midazolam and propofol groups did not differ ($P > 0.05$). Finally, the effects of both drugs on response time dissipated to a similar extent (returning to baseline) over the course of 1 h, despite continuous infusion of the drugs ($P > 0.05$). The initial bolus dose and infusions of both midazolam and propofol produced similar effects on response time, showing that both groups were sedated to the same level throughout the study.

Amnesic effects of propofol and midazolam

Three main analyses were conducted on the memory data. The first compared memory performance for the treatment groups on material presented before the drug was given and tested immediately after the bolus dose of the drugs (during the peak effect). Analysis one, therefore, gave a measure of the effects of drugs on memory retrieval. Analysis two investigated memory for stimuli presented after the first bolus of the drug and tested 1 h later, whilst the subject was still receiving the drug. This analysis provided a measure of the effects of the drugs on memory encoding and storage. Analysis three evaluated subjects' performances during a continuous infusion of the drug after a 7-day drug-free interval and provided a measure of the long-term effects of the drugs. The partially overlapping design also allowed a further test of the possibility that drugs affect the retrieval of information.

Analysis 1. Table II presents the data for recognition and perceptual facilitation for the items that were shown before the drug was given and tested under the influence of the drugs during the first session. It shows no effects of drug condition on either test (all $P > 0.05$). These findings indicate that neither propofol nor midazolam impaired the retrieval processes required for recognition or perceptual facilitation to occur.

Analysis 2. Table III presents the data for recognition and perceptual facilitation for the items that were both presented *and* tested under the influence of the drugs during the first experimental session. It shows that both midazolam and propofol significantly impaired performance on the explicit (recognition) memory test relative to the placebo group ($P < 0.05$). Additionally, midazolam produced significantly greater amnesia than propofol

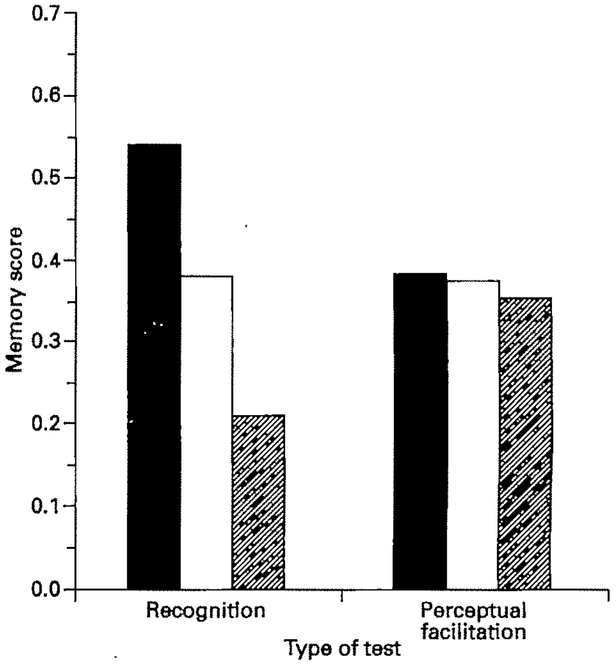


FIG. 2. Recognition and perceptual facilitation for words after a 7-day retention interval by drug condition at encoding. ■ = Placebo; □ = propofol; ▨ = midazolam.

TABLE II. *Recognition and perceptual facilitation scores (mean (SD)) for fragmented words: pre-drug acquisition*

Condition	Recognition (*A*)	Perceptual facilitation
Placebo	0.77 (0.15)	0.48 (0.13)
Propofol	0.78 (0.26)	0.48 (0.12)
Midazolam	0.75 (0.19)	0.41 (0.15)

TABLE III. *Recognition and perceptual facilitation scores (mean (SD)) for fragmented words: post-drug acquisition*

Condition	Recognition (*A*)	Perceptual facilitation
Placebo	0.79 (0.16)	0.46 (0.10)
Propofol	0.68 (0.26)	0.47 (0.16)
Midazolam	0.51 (0.23)	0.38 (0.11)

TABLE IV. *Recognition and perceptual facilitation scores (mean (SD)) for fragmented words: 7-day retention interval*

Condition	Recognition (*A*)	Perceptual facilitation
Placebo	0.54 (0.17)	0.38 (0.18)
Propofol	0.38 (0.24)	0.37 (0.13)
Midazolam	0.21 (0.13)	0.35 (0.17)

TABLE V. *Analysis of state dependency in recognition and memory tests (mean (SD))*

	Overlapping	Non-overlapping
Recognition	0.35 (0.27)	0.44 (0.19)
Perceptual facilitation	0.39 (0.16)	0.35 (0.16)

($P < 0.05$). In contrast, there was no difference between the groups in the implicit memory (perceptual facilitation) test ($P > 0.05$). These analyses suggest that both midazolam and propofol had an effect on recognition memory, but little or no effect on perceptual facilitation. Furthermore, it appears that the amnesic effect of midazolam was more profound than that of propofol.

Analysis 3. The data from the items tested after a 7-day retention interval were analysed according to the subject's condition at the time of stimulus study and at the time of stimulus test. An influence of the drugs on memory storage would be associated with an effect based on the subject's condition at the time of study, whereas an effect on retrieval would be more apparent when the data were analysed according to the subject's condition when tested. The analysis conducted based on the subject's condition at the time of test revealed no significant effects (all $P > 0.05$). This analysis replicates and extends the findings from Analysis 1, in showing that the drugs did not affect memory retrieval.

The findings for the analysis conducted according to the subject's condition at the time of encoding were consistent with the within-drug analyses (see Analysis 2). Table IV presents the results for the three drug conditions. It shows that both midazolam and propofol significantly impaired performance in the explicit (recognition) memory test relative to the placebo group ($P < 0.05$) and that midazolam produced significantly greater amnesia than propofol ($P < 0.05$). There was no difference between groups in the implicit memory (perceptual facilitation) test ($P > 0.05$). These analyses show there was a stepwise amnesic effect on the recognition test with the best performance in the placebo group, an intermediate level of performance in the propofol group, and the most profound amnesia in the midazolam group.

Table V presents the same data in a different form to address the issue of state-dependency. The three groups in which there was an overlap in the conditions on the two days (placebo–placebo, propofol–propofol, midazolam–midazolam) were compared with the four groups in which there was no overlap (placebo–propofol, propofol–placebo, placebo–midazolam, midazolam–placebo). State-dependency would be observed if performance in the overlapping condition was better than performance in the non-overlapping condition. However, there was no difference and so there was no evidence for state-dependent memory effects on either the recognition memory test or the perceptual facilitation test ($P > 0.05$).

DISCUSSION

We have shown that midazolam and propofol had similar cognitive effects. Both drugs increased reponse times to a similar degree after an initial bolus dose of the drug and these effects dissipated to similar extent after 1 h during a continuous i.v. infusion of the drug. These results show that the bolus doses and infusion rates given to the volunteers produced similar levels of sedation throughout the study.

It has been suggested that memory is dependent on the degree of sedation [14, 15]. Despite similar levels of sedation, midazolam and propofol produced different levels of amnesia. On every recognition memory test, performance was worse in the midazolam group than in the propofol group. Furthermore, response times had returned to normal when the material was presented for the 7-day retention interval (Analysis 3). At this time there was evidence of a profound amnesia for both drugs, even though reaction times were normal. These findings show that the amnesic effects could not be attributed to differences in sedation.

Both drugs impaired performance on the explicit recognition memory test, but neither midazolam nor propofol affected performance on the perceptual facilitation (implicit memory) task. Despite this qualitative similarity, midazolam and propofol had different quantitative effects—midazolam produced a more profound amnesia than propofol with the recognition memory tests. This difference in memory performance cannot be attributed easily to greater impairment in general processing produced by midazolam (as reflected by a clinical difference in sedation) because response times for the two groups of subjects were similar.

Both drugs impaired processes associated with the storage or consolidation of new information, and neither drug affected processes associated with retrieval. There was no evidence for a state-dependent memory effect with propofol or midazolam with either task (implicit or explicit memory test), or when all the conditions were combined. Therefore we have shown a selective explicit memory deficit for information that was learned under the influence of the drugs, and that this deficit was more severe for midazolam than for propofol. These results confirm the clinical reports that propofol has amnesic properties [3], but that they are not as profound as those of midazolam.

Work in the area of memory and anaesthesia has suggested the possibility that intraoperative memories can be formed without conscious recollection [16–18]. The apparent inability of midazolam and propofol to impair implicit memory as measured by perceptual facilitation in this study suggests that the formation of such "unconscious" memories cannot be dismissed.

ACKNOWLEDGEMENTS

We thank ICI, Alderley Park, Manchester and ICI Pharma, Paris for their support with funding for this study. R.McC. was supported in part by a grant from Leverhulme Trust to King's College, Cambridge.

REFERENCES

1. Dundee JW, Halliday NJ, Harper KW, Brogden RN. Midazolam: A review of its pharmacological properties and therapeutic use. *Drugs* 1984; **28**: 519–543.
2. O'Boyle C. Benzodiazepine-induced amnesia and anaesthetic practice: A review. In: Hindmarch I, Ott H, eds. *Benzodiazepine Receptor Ligands, Memory and Information Processing*. Berlin: Springer-Verlag, 1988; 146–165.
3. Wilson E, Mackenzie N, Grant IS. A comparison of propofol and midazolam by infusion to provide sedation in patients who received spinal anaesthesia. *Anaesthesia* 1988; 43 (Suppl.): 91–94.
4. Cohen NJ, Squire LR. Preserved learning and retention of pattern-analyzing skill in amnesia: Dissociation of "knowing how" and "knowing that". *Science* 1980; **210**: 207–209.
5. Tulving E. *Elements of Episodic Memory*. Oxford: Clarendon Press, 1983.
6. Tulving E, Schacter DL. Priming and human memory systems. *Science* 1990; **247**: 301–306.
7. Graf P, Schacter DL. Implicit and explicit memory for new associations in normal and amnesic subjects. *Journal of Experimental Psychology: Learning, Memory and Cognition* 1985; **11**: 501–518.
8. Brown MW, Brown J, Bowes JB. Absence of priming coupled with substantially preserved recognition in lorazepam-induced amnesia. *Quarterly Journal of Experimental Psychology* 1989; **41A**: 599–617.
9. Danion J-M, Zimmermann M-A, Willard-Schroeder D, Grange D, Singer L. Diazepam induces a dissociation between explicit and implicit memory. *Psychopharmacology* 1989; **99**: 238–243.
10. Eich E. The cue-dependent nature of state-dependent retrieval. *Memory and Cognition* 1980; **8**: 157–173.
11. Gumerock T, Bub D. *Psychlab* (commercially available software). Montreal: McGill University, 1988.
12. Brown J. *Recognition and Recall*. London: John Wiley & Sons, 1976.
13. Woodworth RS, Schlosberg H. *Experimental Psychology*. London: Methuen & Co. Ltd, 1954.
14. File SE, Lister RG. Do lorazepam-induced deficits in learning result from impaired rehearsal, reduced motivation or increased sedation? *British Journal of Clinical Pharmacology* 1982; **14**: 545–550.
15. Grober E, Leipzig RM, Lipton RB, Wisniewski W, Schroeder M, Davies P, Ritter W, Buschke H. Does scopolamine directly impair memory? *Journal of Cognitive Neuroscience* 1989; **1**: 327–335.
16. Bonke B, Fitch W, Millar K. *Memory and Awareness in Anaesthesia*. Amsterdam: Swets & Zeitlinger, 1990.
17. Evans C, Richardson PH. Improved recovery and reduced post-operative stay after therapeutic suggestions during general anaesthesia. *Lancet* 1988; **8609**: 491–493.
18. Griffiths D, Jones JG. Awareness and memory in anaesthetized patients. *British Journal of Anaesthesia* 1990; **65**: 603–606.

British Journal of Anaesthesia 1993; 70: 617–620

PLASMA CONCENTRATIONS OF MIDAZOLAM AFTER I.V., NASAL OR RECTAL ADMINISTRATION IN CHILDREN

J.-M. MALINOVSKY, C. LEJUS, F. SERVIN, J.-Y. LEPAGE, Y. LE NORMAND, S. TESTA, A. COZIAN AND M. PINAUD

SUMMARY

Midazolam is used frequently for premedication in children, preferably by non-parenteral administration. We have compared plasma concentrations of midazolam after nasal, rectal and i.v. administration in 45 children (aged 2–9 yr; weight 10–30 kg) undergoing minor urological surgery. General anaesthesia consisted of spontaneous respiration of halothane and nitrous oxide in oxygen via a face mask. After administration of atropine and fentanyl i.v., children were allocated randomly to receive midazolam 0.2 mg kg^{-1} by the nasal, rectal or i.v. route. In the nasal group, children received 50 % of the dose of midazolam in each nostril. In the rectal group, midazolam was given rectally via a cannula. Venous blood samples were obtained before and up to 360 min after administration of the drug. Plasma concentrations of midazolam were measured by gas chromatography and electron capture detection. After nasal and rectal administration, midazolam Cmax was 182 (SD 57) ng ml^{-1} within 12.6 (5.9) min, and 48 (16) ng ml^{-1} within 12.1 (6.4) min, respectively. Rectal administration resulted in smaller plasma concentrations. In the nasal group, a plasma concentration of midazolam 100 ng ml^{-1} occurred at about 6 min. After 45 min, the concentration curves after i.v. and nasal midazolam were similar. (Br. J. Anaesth. 1993; **70**: 617–620)

KEY WORDS
Hypnotics, benzodiazepines: midazolam.

In children, fear of venepuncture and separation from parents may produce stormy induction of anaesthesia [1]. In these circumstances, premedication helps to decrease anxiety and minimize psychological trauma [2]. Various premedications and delivery systems have been developed using different routes of administration.

Benzodiazepines are used routinely for premedication in children [3, 4]. Most of these drugs have prolonged effects associated with slow elimination. Midazolam, a water soluble, short-acting 1,4-benzodiazepine, with a rapid elimination in adults, is frequently used in children as premedication by the i.m. [3], rectal [4] or oral [5] route. Pharmacokinetic studies of midazolam administered by these routes have shown slow onset [5], small peak plasma concentrations [4, 5] and low bioavailability [4, 5].

Nasal administration has been described for sufentanil [6], ketamine [7] and midazolam [8]. For nasal midazolam, there is only one report of plasma concentrations over 90 min in children during general anaesthesia [9]. The aim of this study was to compare plasma concentrations of midazolam administered after nasal, rectal and i.v. administration in healthy children.

METHODS AND PATIENTS

After obtaining institutional approval and informed consent of parents, we studied 45 ASA I children (ages 2–9 yr; weights 10–30 kg) undergoing minor urological surgery. Exclusion criteria were rhinopharyngitis, digestive disorders, treatment with theophylline, H_2 receptor antagonists, β-lactamines associated with clavulanic acid and aminoglycosides, and anaesthetic procedures involving barbiturate administration.

Anaesthesia was induced with halothane and nitrous oxide in oxygen via a face mask. Anaesthesia was maintained with halothane (expired concentration approximately 1 %) without tracheal intubation. After cannulation of a vein using a 20-gauge cannula and i.v. injection of fentanyl 2 μg kg^{-1} and atropine 15 μg kg^{-1}, midazolam was administered. Children were allocated randomly to three groups: group N ($n = 15$) received nasal midazolam 0.2 mg kg^{-1} as reported previously [8]; group V ($n = 15$) received i.v. midazolam 0.2 mg kg^{-1}; and group R ($n = 15$) received rectal midazolam 0.2 mg kg^{-1}. The drug was diluted in saline solution to a 0.1 % concentration for all routes. In group N, 50 % of each dose was administered (a few drops) in each

---

JEAN-MARC MALINOVSKY*, M.D., CORINNE LEJUS, M.D., JEAN-YVES LEPAGE, M.D., SAMIA TESTA, M.D., ANTOINE COZIAN, M.D., MICHEL PINAUD, M.D., PH.D. (Département d'Anesthésie-Réanimation Chirurgicale); YVES LE NORMAND, M.D. (Laboratoire de Pharmacologie Clinique); Hôtel-Dieu, CHRU, B.P. 1005, 44035 Nantes Cédex 01, France. FRÉDÉRIQUE SERVIN, M.D., Département d'Anesthésie-Réanimation Chirurgicale, Hôpital Bichat, 46 rue Henri Huchard, 75018 Paris, France.
Accepted for Publication: January 21, 1993.

*Address for correspondence: Département d'Anesthésie-Réanimation Chirurgicale, Centre Hospitalier et Universitaire de Nantes, 1 place Ricordeau, 44035 Nantes Cedex 01, France.

nostril within 15 s. Rectal administration was performed using a short, air-washed cannula. After i.v. administrations, the cannula was flushed with physiological saline 10 ml. In all groups, heart rate, arterial pressure, ventilatory frequency and finger pulse oximetry were monitored continuously.

Venous blood samples (3 ml) were obtained before administration and 2, 4, 6, 8, 10, 15, 20, 30, 45, 60, 120, 180, 240 and 360 min after administration of midazolam. Plasma was separated by centrifugation at 4500 *g* and stored at -20 °C until analysis. Plasma concentration of midazolam was measured by gas–liquid chromatography (Delsi model 300 gas chromatograph, Delsi-Nermag Instrument, Argenteuil, France) using an adaptation of clonazepam microdetermination with capillary column and electron-capture detection [9]. Internal standard was prazepam. The smallest value measured was 1 ng ml^{-1} in plasma, with a single deposit and a signal-to-noise ratio of 2:1. The calibration curve was linear within the range 0–200 ng ml^{-1}. Greater concentrations required dilution of plasma samples before extraction. The main metabolite of midazolam, α-hydroxymidazolam, was not detected by the assay. The coefficients of variation were less than 7% (intraassay and interassay).

Statistical comparisons were carried out by ANOVA for continuous variable (age, weight, *C*max and *t*Cmax). $P < 0.05$ was considered significant.

RESULTS

Patient characteristics are listed in table I. No child experienced nasal disturbances and after rectal midazolam there was no defaecation or rectal lesion. There were no significant haemodynamic changes in the three groups after administration of midazolam. Ventilatory frequency was not reduced significantly 5 min after nasal or i.v. administration, and was unchanged throughout in group R. One of the 15 children had apnoea after i.v. administration of midazolam and required manually assisted ventilation for 5 min. No child had prolonged sedative effects after operation. In group V, three of 15, and in group R two out of 15, were excluded because of blood collection difficulties after 30 min.

*C*max and *t*Cmax in all groups are presented in table II. Figure 1 represents logarithmic concentration *vs* time curves after all routes of admin-

TABLE I. *Characteristics of children and surgical procedures in each group (mean (range or* SD*) or number). No significant difference between groups*

	Group N	Group V	Group R
Age (yr)	3.6 (2–9)	4.5 (2–7)	4.2 (2–7)
Weight (kg)	16.1 (3.9)	19.4 (5.1)	16.5 (4)
Surgical procedures (No.)			
Hypospadias	2	1	2
Circumcision	10	7	3
Herniorrhaphy	1	5	5
Testis surgery	2	2	5

TABLE II. *Cmax and* t*Cmax in children receiving midazolam 0.2 mg kg^{-1} nasally (group N), i.v. (group V) or rectally (group R).* $P < 0.001$ *: ***compared with groups N and R; ††† compared with group R*

	Group N		Group V		Group R	
Patient No.	*C*max (ng ml^{-1})	*t*Cmax (min)	*C*max (ng ml^{-1})	*t*Cmax (min)	*C*max (ng ml^{-1})	*t*Cmax (min)
1	128	8	2226	2	55	20
2	311	10	840	2	62	6
3	161	20	922	2	71	10
4	261	10	1030	2	36	10
5	205	15	3805	2	68	15
6	207	15	3357	2	33	8
7	112	10	692	2	72	30
8	129	10	844	2	34	10
9	138	8	400	2	25	8
10	237	8	658	2	44	15
11	140	30	1770	2	32	30
12	152	20	939	2	48	15
13	192	15	—	—	45	20
14	152	10	—	—	—	—
15	217	10	—	—	—	—
Mean	182†††	12.6	1457***	2	48	12.1
SD	57	5.9	1114		16	6.4

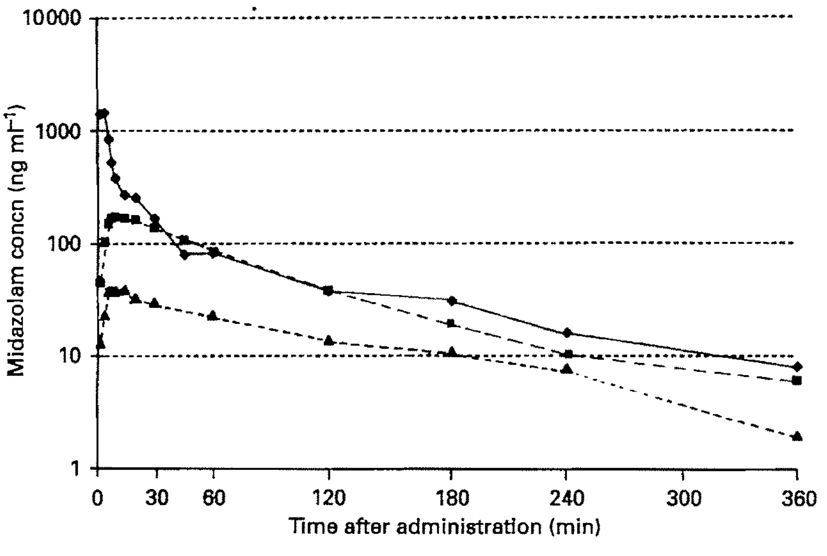


FIG. 1. Mean midazolam plasma concentration–time logarithmic curves after midazolam 0.2 mg kg^{-1} in children. ◆ = Group V (i.v.); ■ = group N (nasal); ▲ = group R (rectal).

istration, expressed as the mean values for each group. After 45 min, plasma concentration *vs* time curves in groups N and V were similar.

DISCUSSION

The present study is the first in which plasma concentrations of midazolam have been compared after i.v., nasal and rectal administration in children. Previous studies examined only one of these routes. Walberg, Wills and Eckert measured plasma concentrations after a smaller dose of midazolam (0.1 mg kg^{-1}) administered nasally in children undergoing cardiac surgery and blood samples were obtained for only 90 min after administration [10]. Saint-Maurice and colleagues studied rectal midazolam 0.3 mg kg^{-1} premedication in 16 children, but pharmacokinetic data were obtained in only nine, and there was no comparison with venous administration [4].

In the present study, anaesthesia comprised nitrous oxide, halothane and fentanyl. Halothane causes a decrease in hepatic blood flow and modification of hepatic enzyme function [11], and this may influence the metabolism of midazolam, increasing its plasma concentrations. Plasma concentrations may also be greater after nasal administration during general anaesthesia compared with awake children because midazolam is irritant. Nasal administration during general anaesthesia avoids coughing and sneezing with expulsion of part of the dose, so that if nasal absorption is not complete, the agent may be absorbed partly via the oral route. However, the supine position on the operating table produces nasal stasis and complete absorption via the nasal mucosa without any first pass hepatic metabolism.

Plasma concentrations were similar in groups N and V from 45 min after administration. In group R, plasma concentrations were constantly less than those in the two other groups, possibly because of first pass metabolism. The large variation in rectal pH in children may cause modification in chemical properties and altered absorption [12]. Most maturational changes occur within the first 1 yr of life, so that hepatic metabolism in older children is similar to that of adults.

The individual threshold plasma concentration of midazolam for sedation varies in the range 30–100 ng ml^{-1} in adults [13], but has not been determined in children. However, Wilton and colleagues [8] noted a calming effect within 5 min after nasal midazolam 0.2 mg kg^{-1} and this became significant within 10 min. Wilton's group used nasal midazolam 0.2 and 0.3 mg kg^{-1} as premedication [8] and found that the degree of sedation was similar. However, the 0.3-mg kg^{-1} dose required a larger volume, resulting in some expulsion of part of the dose. In our study with a nasal dose of 0.2 mg kg^{-1}, plasma concentrations reached 100 ng ml^{-1} or more within 6 min, *t*Cmax occurring at about 12 min.

The main metabolite of midazolam, α-hydroxymidazolam, which was not detected by our assay, has sedative properties and may facilitate rapid onset of sedation. As absorption via nasal mucosa is determined by the physical and chemical properties of a solution, the absorption of midazolam may differ when a lipophilic vehicle is used (the drops in our study contained a hydrophilic solution). Secretions caused by nasal irritation may also modify absorption, but rhinitis was not observed in our study, and all the children received atropine before midazolam was administered.

In children who received rectal midazolam, the time to reach a sedative threshold of 100 ng ml^{-1} was longer than that after nasal administration [4]. Yaster and colleagues [14] recommended a dose of midazolam up to 1 mg kg^{-1}, and Saint-Maurice and colleagues [4], using a dose of 0.3 mg kg^{-1}, observed a sedative effect within 20 min, with a *C*max of 100 ng ml^{-1} within 16 min. In the present study, plasma concentrations in group R were always less than 100 ng ml^{-1}. The smaller plasma concentrations after rectal administration may have been caused by first pass metabolism. Other agents such as ketamine may be administered rectally and the plasma concentrations [15] reflect first-pass hepatic metabolism so that the ketamine metabolite, norketamine, is present in greater concentrations than ketamine.

The plasma concentrations of midazolam were similar to those of sufentanil after nasal administration (*t*Cmax at about 10 min, *C*max 67% less than after i.v. administration) [6]. We found that, within 10 min after nasal midazolam, plasma concentrations were greater than 180 ng ml^{-1}, as great as plasma concentrations obtained within 30 min after i.m. [2] or oral [3] midazolam 0.2 mg kg^{-1}.

Our results in this pharmacokinetic study suggest that nasal administration of midazolam may be worth investigating for rapid premedication in children.

REFERENCES

1. Meursing AEE. Psychological effects of anaesthesia in children. *Current Opinion in Anaesthesiology* 1989; 2: 335–338.
2. Kanto J. Midazolam: the first water-soluble benzodiazepine. Pharmacology, pharmacokinetics and efficacy in insomnia and anesthesia. *Pharmacotherapy* 1985; 5: 138–155.
3. Taylor MB, Vine PR, Hatch DJ. Intramuscular midazolam premedication in young children. *Anaesthesia* 1986; 41: 21–26.
4. Saint-Maurice C, Meistelman C, Rey E, Esteve C, de Lauture D, Olive G. The pharmacokinetics of rectal midazolam for premedication in children. *Anesthesiology* 1986; 65 536–538.
5. Allonen H, Ziegler G, Klotz U. Midazolam kinetics. *Clinical Pharmacology and Therapeutics* 1981; 30: 653–661.
6. Helmers JH, Noordium H, Van Peer A, Van Leeuwen L, Zurmond WW. Comparison of intravenous and intranasal sufentanil absorption and sedation. *Canadian Journal of Anaesthesia* 1989; 36: 494–497.
7. Aldrete JA, Roman-de Jesus JC, Russell LJ, D'Cruz O. Intranasal ketamine as induction adjunct in children: preliminary report. *Anesthesiology* 1987; 67: A514.
8. Wilton NC, Leigh J, Rosen DR, Pandit UA. Preanesthetic sedation of preschool children using intranasal midazolam. *Anesthesiology* 1988; 69: 972–975.
9. Edelbroek PM, Wolff FA. Improved microdetermination of underivatized clonazepam in serum by gas chromatography. *Clinical Chemistry* 1981; 24: 1774–1777.
10. Wallberg EJ, Wills RJ, Eckert J. Plasma concentrations of midazolam in children following intranasal administration. *Anesthesiology* 1991; 74: 233–235.

11. Reilly CS, Wood AJJ, Koshakji RP, Wood M. The effect of halothane on drug disposition: contribution of changes in intrinsic drug metabolizing capacity and hepatic blood flow. *Anesthesiology* 1985; **63**: 70–76.
12. Jantzen JP, Tzanova I, Witton PK, Klein AM. Rectal pH in children. *Canadian Journal of Anaesthesia* 1989; **36**: 665–667.
13. Crevoisier CH, Eckert M, Heizmann P, Thurneysen DJ, Ziegler WH. Relation between the clinical effect and the pharmacokinetics of midazolam following i.m. and i.v. administration. *Arzeimittel Forschung* 1981; **31**: 2211–2215.
14. Yaster M, Berkowitz ID, Bender KS, Maxwell LG, Nichols DG. Rectally administered midazolam for preinduction of anesthesia in children. *Anesthesiology* 1989; 71: A1043.
15. Idvall J, Holasek J. Rectal ketamine for induction of anaesthesia in children. *Anaesthesia* 1983; **38**: 60–64.

British Journal of Anaesthesia 1993; **70**: 621–625

TRANSOESOPHAGEAL ECHOCARDIOGRAPHIC ASSESSMENT OF HAEMODYNAMIC FUNCTION DURING LAPAROSCOPIC CHOLECYSTECTOMY†

A. J. CUNNINGHAM, J. TURNER, S. ROSENBAUM AND T. RAFFERTY

SUMMARY

We have measured cardiovascular changes associated with insufflation of carbon dioxide and the reverse Trendelenburg position during laparoscopic cholecystectomy, using transoesophageal echocardiography in 13 healthy patients. End-tidal carbon dioxide values increased after insufflation of carbon dioxide, with values significantly ($P < 0.05$) increased after lateral tilt positioning. Creation of a pneumoperitoneum was associated with increases ($P < 0.05$) in left ventricular end-systolic wall stress, concomitant with increases ($P < 0.01$) in peak airway pressure and systemic arterial pressure. In addition, left ventricular end-diastolic area decreased ($P < 0.05$) after reverse Trendelenburg positioning. Left ventricular ejection fraction was maintained throughout the study. (Br. J. Anaesth. 1993; **70**: 621–625)

KEY WORDS

Measurement techniques: transoesophageal echocardiography. Surgery: laparoscopic cholecystectomy.

Laparoscopic cholecystectomy, described first by Phillipe Mouret in 1988 [1], was reported first in the literature by Perissat, Collet and Belliard [2] and refined and popularized in the United Kingdom by Nathanson, Shimi and Cuschiei [3]. Laparoscopic cholecystectomy has been reported to have the advantages of shorter hospital stay, more rapid return to normal activities, less pain associated with the small, limited incisions and less postoperative ileus compared with open laparotomy [4–6].

Indications for the procedure soon became more liberal after case reports confirmed its efficacy in patients with acute cholecystitis, and in association with obesity, pregnancy and previous abdominal surgery [7–9]. The laparoscopic surgical technique has been advocated for older patients who may have co-existing cardiac or pulmonary disease, or both [10]. Laparoscopic cholecystectomy involves longer periods of intraperitoneal insufflation of carbon dioxide than gynaecological procedures.

The objectives of this study were to assess changes in venous return, myocardial performance and afterload, as determined by transoesophageal echocardiographic assessment of left ventricular end-diastolic area (EDA), left ventricular ejection fraction (LVEF) and left ventricular end-systolic wall stress (LVESWS) in healthy patients undergoing laparoscopic cholecystectomy.

PATIENTS AND METHODS

After obtaining local Human Investigation Committee approval, we studied 13 healthy patients (ASA physical status I–II) undergoing laparoscopic cholecystectomy. All patients gave informed consent. Patients with a history or ECG changes suggestive of previous myocardial infarction or evidence of left ventricular dysfunction were excluded, as were patients with disease states that might preclude transoesophageal echocardiography—coagulation or bleeding diathesis and oesophageal pathology.

A standard anaesthetic technique was used for all patients. All subjects were admitted to hospital on the morning of surgery. Midazolam 1–3 mg was administered i.v. for preoperative sedation before induction of anaesthesia with thiopentone 4.0 mg kg^{-1} i.v.; vecuronium 0.1 mg kg^{-1} i.v. was given to facilitate tracheal intubation. Anaesthesia was maintained with 0.5–1.0% end-tidal isoflurane and 50% oxygen in air, with incremental bolus doses of i.v. fentanyl 1–2 μg kg^{-1}. A urinary bladder catheter and nasogastric tube were inserted.

Intraoperative monitoring included continuous ECG (leads II and V_5), systemic arterial pressure using an automated cuff (PCMS system, Spacelabs Inc., Redmond, WA), pulse oximetry (Spacelabs Inc., Redmond, WA), neuromuscular function, inspired oxygen fraction, peak airway pressure, oesophageal temperature and urinary output. Intermittent positive pressure ventilation (IPPV) was used using an Ohmeda 7810 volume cycled ventilator (BOC Healthcare Co., Madison WI), with an inspiratory flow rate of 25 litre min^{-1}, a ventilatory

---

Anthony J. Cunningham*, M.D., F.R.C.P.C.; John Turner, M.D.; Stanley Rosenbaum, M.D.; Terence Rafferty, M.D.; Department of Anesthesiology, Yale University School of Medicine, New Haven, CT 06510, U.S.A. Accepted for Publication: January 22, 1993.

*Present address, for correspondence: Department of Anaesthesia, Professorial Unit, Beaumont Hospital, Dublin 9, Ireland.

†This study was presented, in part, at the European Academy of Anaesthesiology Annual Meeting, Pozman, Poland August 1992 and the International Anesthesia Research Society Meeting, San Diego, California, U.S.A. March 1993.

frequency of 8 b.p.m., a tidal volume of 100 ml kg^{-1} and an inspiratory:expiratory (I:E) ratio of 1:2. A Perkins–Elmer Advantage mass spectrometer was used to measure end-tidal carbon dioxide tension (PE'_{CO_2}) and isoflurane concentrations. End-tidal isoflurane concentrations were maintained in the range 0.5–1.0%.

The operative technique involved i.p. insufflation of carbon dioxide via a Verres needle inserted into a small infra-umbilical incision, with the patient in a 15–20° Trendelenburg position. An electronic variable-flow insufflator terminated flow when an intra-abdominal pressure of 15 mm Hg was reached. A cannula was inserted in place of the needle to provide and maintain insufflation adequate for surgery. A video laparoscope was inserted through the cannula and the operative field was visualized. The patient's position was changed to steep reverse Trendelenburg, with left lateral tilt, to facilitate retraction of the gall bladder fundus. The cystic duct and cystic artery were identified and clamped. The gall bladder was removed by instruments introduced through canulae via three additional small (5–11 mm) skin incisions, including one to the right of the midline to avoid the falciform ligament and two right upper quadrant sites.

Heart rate (HR), systolic/diastolic and mean arterial pressures (SAP/DAP and MAP), and arterial oxygen saturation (Sp_{O_2}) were recorded 3 min before induction of anaesthesia. These variables, in addition to peak airway pressures and PE'_{CO_2} were also recorded at the following times: 3 min after induction of anaesthesia; 3 min before carbon dioxide insufflation; 1, 3 and 5 min after insufflation; after reverse Trendelenburg positioning and after left lateral tilt.

Two-dimensional echocardiographic data were obtained with a 5-MHz (64-element) transoesophageal, transverse plane phased array transducer (Imaging System 77020 Hewlett–Packard Corporation, Andover, MA) inserted after induction of anaesthesia and tracheal intubation. Transgastric short axis images were obtained at the previously described left ventricular mid papillary muscle level [11]. Image clarity was optimized by grey scale adjustment.

Measured variables included left ventricular cavity end-diastolic and end-systolic planimetered areas (EDA and ESA) [12] and M-mode determined end-systolic posterior and anterior wall thickness (WT). Derived variables included left ventricular ejection fraction (LVEF) and left ventricular end-systolic meridional wall stress (LVESWS) [13, 14]. An average of three consecutive sinus beats at end expiration was obtained for each value of EDA and ESA. End-diastole was indicated by the peak of the ECG R wave and end-systole was defined as the smallest endocardial area. Left ventricular ejection fraction was determined by the calculation ((EDA − ESA) × 100)/EDA. LVESWS was calculated by the formula: $0.334 \times P\ (D)/WT\ (1 + WT/D)$, where P = cuff systolic arterial pressure; D = left ventricular diameter and WT = wall thickness represented by the average of the anterior and posterior measurements.

Videotapes recorded in real time simultaneously with 1-cm calibration grids and an electrocardiogram were reviewed on an off-line analyser system providing forward, reverse, slow motion and freeze viewing formats. The areas of interest were traced by hand-held digitizer. Echocardiographic data were obtained before insufflation of carbon dioxide; 1, 3 and 5 min after insufflation; after reverse Trendelenburg position and after left lateral tilt. Measurement reproducibility was assessed by randomly selecting 25% of profiles for reanalysis. Intra- and interobserver variabilities did not exceed 8% and 12%, respectively.

Statistical methods

Paired Student's *t* tests and Pearson correlation coefficients were used to compare measured and derived cardiovascular and echocardiographic values before insufflation of carbon dioxide with values 1, 3 and 5 min after insufflation and after reverse Trendelenburg and lateral tilt position changes. Results are expressed as mean (SD). $P < 0.05$ was considered statistically significant.

RESULTS

We studied 13 patients (five male). Patients' mean age was 52 (17) yr (range 22–78 yr). The mean height and weight were 168 (8) cm and 80 (10) kg, respectively. Preinduction HR was 74 (17) beat min^{-1}, SAP 147 (21) mm Hg, DAP 83 (11) mm Hg, MAP 107 (16) mm Hg and Sp_{O_2} 97 (2)%.

There were no significant changes in either heart rate or arterial oxygen saturation after insufflation of carbon dioxide and changes in patient position. SAP, DAP and MAP were significantly ($P < 0.01$) greater 1, 3 and 5 min after insufflation of carbon dioxide, reverse Trendelenburg and lateral position changes, compared with the pre-insufflation values. PE'_{CO_2} values were greater after insufflation of carbon dioxide, but the values were significantly ($P < 0.05$) increased only after the lateral tilt position change. Peak airway pressures were significantly ($P = 0.0001$) greater than pre-insufflation values at 1, 3 and 5 min after insufflation and after reverse Trendelenburg and lateral tilt positioning (table I).

Left ventricular ESA and LVEF were unchanged after insufflation of carbon dioxide and changes in patient position. Left ventricular EDA were unchanged after insufflation. Left ventricular EDA were significantly ($P < 0.05$) reduced after reverse Trendelenburg positioning. LVESWS increased after carbon dioxide insufflation. The increase in LVESWS was statistically significant ($P < 0.05$) 3 min after the insufflation.

A significant linear correlation was observed between MAP and LVESWS before insufflation of carbon dioxide and 3 and 5 min after insufflation and reverse Trendelenburg position ($r = 0.74$, 0.64 and 0.67, respectively). Similarly, significant linear correlations were recorded between the variables MAP and peak airway pressure before carbon dioxide insufflation and 5 min after insufflation and reverse Trendelenburg position ($r = 0.63$ and 0.79, respectively).

TABLE I. *Measured and derived haemodynamic and echocardiographic data. Significant differences—compared with before carbon dioxide*: $^{*}P < 0.05$, $^{**}P < 0.01$; *compared with 5 min after carbon dioxide*: $^{\dagger}P < 0.05$

	Before CO_2 insufflation	After CO_2 insufflation 1 min	3 min	5 min	Reverse Trendelenburg	Lateral tilt
Heart rate (beat min^{-1})	69 (16)	70 (17)	74 (12)	71 (10)	71 (12)	70 (12)
SAP (mm Hg)	110 (13)	131 (19)**	146 (20)**	147 (23)**	151 (21)*	148 (24)**
DAP (mm Hg)	67 (16)	85 (10)**	94 (12)**	97 (12)**	98 (12)**	94.92 (12)**
MAP (mm Hg)	81 (11)	100 (13)**	111 (14)**	115 (13)**	116 (14)**	111 (14)**
Sp_{O_2} (%)	98 (1)	98 (1)	98 (1)	98 (2)	98 (1)	98 (2)
$P\acute{E}_{CO_2}$ (kPa)	3.7 (0.4)	3.6 (0.8)	3.7 (0.8)	3.7 (0.7)	3.9 (0.7)	4.1 (0.7)*
Peak airway pressure (cm H_2O)	22 (5)	27 (5)**	31 (7)**	31 (6)**	30 (6)**	30 (5)**
Left ventricular end systolic area (cm^2)	18.23 (10.14)	16.92 (7.77)	19.04 (9.15)	19.96 (11.11)	17.94 (10.44)	18.05 (8.04)
Left ventricular end diastolic area (cm^2)	34.26 (15.09)	34.15 (11.44)	35.17 (11.44)	39.94 (15.53)	31.90 (12.96)†	34.44 (13.64)
Left ventricular ejection fraction (%)	48.59 (14.54)	47.20 (17.67)	47.54 (15.30)	50.15 (15.43)	45.98 (11.52)	48.71 (11.47)
Left ventricular end systolic wall stress (dyn cm^{-2})	234 (161)	258 (139)	306 (157)**	311 (160)	297 (137)	295 (135)

DISCUSSION

We found that left ventricular function, as determined by transoesophageal echocardiographic estimation of ejection fraction, was preserved after insufflation of carbon dioxide and changes in patient position, despite variations in loading conditions. However, insufflation of carbon dioxide was associated with increases in left ventricular end-systolic wall stress, concomitant with increases in systemic arterial pressure. In addition, LVEDA decreased after reverse Trendelenburg positioning, while LVEF was maintained. However, it might be speculated that the changes in left ventricular loading conditions might have had deleterious consequences in patients with significant cardiovascular disease.

Laparoscopic cholecystectomy has four potential causes of major physiological changes in the anaesthetized patient—the initial Trendelenburg position, creation of a pneumoperitoneum, the potential for systemic absorption of carbon dioxide, and the reverse Trendelenburg position. Considering the widespread adoption of laparoscopic cholecystectomy, there is a remarkable paucity of data on the haemodynamic and respiratory changes in normal patients and those with cardiorespiratory disorders associated with these manoeuvres. Lack of critical experimental and clinical assessment of the physiological changes associated with laparoscopic cholecystectomy is in marked comparison with data obtained during gynaecological laparoscopy [15, 16].

In laparoscopic procedures, patients are normally placed in a 10–20° Trendelenburg position to keep the small bowel and colon out of the pelvis and to minimize complications associated with blind trocar insertion. Gravity may exert profound effects on the cardiovascular and pulmonary systems. The physiological effects of the Trendelenburg position have been reviewed by Wilcox and Vandam [17]. The associated cardiovascular changes may be influenced by the extent of the head-down tilt, the patient's age, intravascular volume status, associated cardiac disease, anaesthetic drugs and ventilation techniques. However, in our patients, the adoption of the Trendelenburg position was not associated with significant cardiovascular changes, but reverse Trendelenburg positioning was associated with a decrease in indices of left ventricular preload, presumably reflecting a gravitational effect on venous return [18].

The cardiovascular and respiratory changes associated with creation of a pneumoperitoneum have been extensively studied in gynaecological patients. Marshall and colleagues [19] reported no significant changes in cardiac output in anaesthetized, spontaneously breathing patients in whom the intra-abdominal pressure (IAP) was 15–20 cm H_2O (11–15 mm Hg). Smith and colleagues [20] studied the cardiovascular effects of stepwise increases of IAP up to a maximum of 25 cm H_2O in anaesthetized patients undergoing mechanical ventilation. At 25-cm H_2O IAP and increased airway pressure, intrathoracic pressure (ITP), central venous pressure (CVP) and femoral venous pressure were accompanied by hypertension, tachycardia and increased end-tidal carbon dioxide tensions. Based on data obtained from a study of the effects of progressively increasing IAP in horizontal and tilted anaesthetized patients undergoing mechanical ventilation, Kelman and colleagues [21] claimed that moderate increases in IAP (up to 25 cm H_2O) may be accompanied by increased transmural cardiac filling pressure and cardiac output. When IAP was increased further to 40 cm H_2O, tachycardia, hypotension, reduced CVP and cardiac output were observed. These changes were most marked in the horizontal compared with the head-down tilt position. The authors speculated that increased IAP may have two opposite effects on the cardiovascular system—it may force blood out of the abdominal organs and inferior vena cava into the central venous reservoir and may also dam blood back in the legs and thus tend to decrease the central blood volume.

Thus only minor haemodynamic changes occurred during gynaecological laparoscopic procedures with insufflation of carbon dioxide when IAP did not exceed 25 cm H_2O (18 mm Hg). However, these short-duration studies were performed in young, relatively healthy, females in the Trendelenburg position. In our study of older, anaesthetized patients undergoing laparoscopic cholecystectomy, IAP of 15 mm Hg in the reverse Trendelenburg position was associated with increased peak airway pressures, arterial pressure and left ventricular afterload. This study and the limited data available on laparoscopic cholecystectomy suggest that the haemodynamic and respiratory function changes may differ from those reported with gynaecological laparoscopic procedures. In our study, end-tidal carbon dioxide partial pressure increased progressively with time—a finding consistent with data reported by Liu and colleagues [22] and Wittgen and colleagues [23], who demonstrated similar increases in end-tidal carbon dioxide coincident with parallel changes in arterial partial pressures of carbon dioxide during laparoscopic cholecystectomy. Intraoperative hypercapnia may cause increases in plasma catecholamine concentrations, and increases in systemic arterial pressure and cardiac performance [24]. The latter were manifested by a shortened pre-ejection period (PEP), left ventricular ejection time (LVET), and decreased PEP:LVET ratio. Such neurohumoral mechanisms may have contributed to the increases in afterload observed in our study, and the preservation of cardiac performance in the face of these changes.

Systemic arterial pressure was measured using an automated cuff. Such automatic oscillometric measurements have been shown to correlate closely with invasive arterial cannulation and auscultation determinations [25, 26]. End-tidal carbon dioxide tension and oximetry were used as non-invasive substitutes for arterial $P\text{CO}_2$ and $P\text{O}_2$ in evaluating adequacy of ventilation and oxygenation. It is well recognized that end-tidal carbon dioxide partial pressure may differ considerably from Pa_{CO_2} because of ventilation–perfusion mismatching [27]. However, in a study of healthy patients undergoing laparoscopic cholecystectomy, Liu and colleagues [22] observed equal and proportional increases in $P\text{E}'_{\text{CO}_2}$ and Pa_{CO_2} after insufflation of carbon dioxide.

The variables LVEDA, LVEF and LVESWS were measured by transoesophageal echocardiography (TOE). Clements and colleagues [28] and Urbanowitz and colleagues [29] have demonstrated a close correlation between TOE-derived estimates of EDA and LVEF and radionuclide measurements. LVESWS is a quantitative index of left ventricular afterload [13]. In our study, these afterload estimates were based on LV echocardiographic end-systolic diameter (D), wall thickness (WT) and systolic arterial pressure (P), calculated by the formula: $0.334 \times \text{P(D)/WT}\ (1 + \text{WT/D})$ and expressed as dyn cm^{-2}. O'Kelly and colleagues [13] have validated the use of TOE measurements in this context. Quinones and colleagues [14] have reported that LVESWS determinations with arterial pressure cuff systolic pressure measurements correlate closely ($r = 0.97$) with determinations using invasive end-systolic LV micromanometer pressure in patients with chronically sustained hypertension. Reichek and colleagues [30] similarly validated the technique before and after load manipulation with nitroglycerin, nitroprusside, phenylephrine and saline.

It should be noted that our data were obtained in healthy patients. Further studies may be warranted in patients with cardiopulmonary disease.

REFERENCES

1. Way LW. Changing therapy for gallstone disease. *New England Journal of Medicine* 1990; **323**: 1273–1274.
2. Perissat J, Collet DR, Belliard R. Gallstones: laparoscopic treatment, intracorporeal lithotripsy followed by cholecystectomy or cholecystectomy—a personal technique. *Endoscopy* 1990; **21**: 373–374.
3. Nathanson LK, Shimi S, Cuschieri A. Laparoscopic cholecystectomy: the Dundee technique. *British Journal of Surgery* 1991; **78**: 155–159.
4. Dubois F, Icard P, Berthelot G, Levard H. Coelioscopic cholecystectomy: preliminary report of 36 cases. *Annals of Surgery* 1990; **211**: 60–62.
5. Grace PA, Quereshi A, Coleman J, Keane R, McEntee G, Broe P, Osborne H, Bouchier-Hayes D. Reduced postoperative hospitalization after laparoscopic cholecystectomy. *British Journal of Surgery* 1991; **78**: 160–162.
6. Jones RM, Fletcher DR, McLellan DG, Lowe AW, Hardy KJ. Laparoscopic cholecystectomy: initial experience. *Australian and New Zealand Journal of Surgery* 1991; **61**: 261–266.
7. Flowers JL, Bailey RW, Scovill WA, Zucker KA. The Baltimore experience with laparoscopic management of acute cholecystitis. *American Journal of Surgery* 1991; **161**: 388–392.
8. Pucci RO, Seed RW. Case report of laparoscopic cholecystectomy in the third trimester of pregnancy. *American Journal of Obstetrics and Gynecology* 1991; **165**: 401–402.
9. Wilson P, Leese T, Morgan WP, Kelly JF, Brigg JK. Elective laparoscopic cholecystectomy for "all-comers". *Lancet* 1991; **338**: 795–797.
10. Dubois F, Berthelot G, Levard H. Laparoscopic cholecystectomy: historical perspective and personal experience. *Surgical Laparoscopy and Endoscopy* 1991; **1**: 52–57.
11. Steward JB, Khandheria BK, Oh JK, Abel MD, Hughes RW, Edwards WD, Nichols BA, Freman WK, Tajik AJ. Transesophageal echocardiography: technique, anatomic correlations, implementation, and clinical applications. *Mayo Clinic Proceedings* 1988; **63**: 650–680.
12. Wyatt HL, Haendchen RV, Meerbaun S, Corday E. Assessment of quantitative measurements for two dimensional echocardiography. *American Journal of Cardiology* 1983; **52**: 369–401.
13. O'Kelly BF, Tubau JF, Knight AA, London MJ, Verrier ED, Mangano DT and the SPI Research Group. Measurement of left ventricular contractility using transesophageal echocardiography in patients undergoing coronary artery bypass grafting. *American Heart Journal* 1991; **122**: 1040–1049.
14. Quinones MA, Mokotoff DM, Nouri S, Winters WL, Miller RD. Noninvasive quantification of left ventricular wall stress: validation of method and application to assessment of chronic pressure overload. *American Journal of Cardiology* 1980; **45**: 782–790.
15. Seed RF, Shakespear TF, Muldoon MJ. Carbon dioxide homeostasis during anaesthesia for laparoscopy. *Anaesthesia* 1970; **25**: 223–231.
16. Hodgson C, McClelland RMA, Newton JR. Some effects of peritoneal insufflation of carbon dioxide at laparoscopy. *Anaesthesia* 1970; **25**: 382–385.
17. Wilcox SW, Vandam LD. Alas, poor Trendelenburg and his position! A critique of its uses and effectiveness. *Anesthesia and Analgesia* 1988; **67**: 574–578.
18. Schiller WR. The Trendelenburg position. Surgical requirements. In: Martin JT, ed. *Positioning in Anesthesia and Surgical Requirements*. Philadelphia: W.B. Saunders, 1987; 112–126.
19. Marshall RL, Jebson PJR, Davie IT, Scott DB. Circulatory

effects of carbon dioxide insufflation of the peritoneal cavity for laparoscopy. *British Journal of Anaesthesia* 1972; **44**: 680–684.

20. Smith I, Benzie RJ, Gordon NLM, Kelman GR, Swapp GH. Cardiovascular effects of peritoneal insufflation of carbon dioxide for laparoscopy. *British Medical Journal* 1971; **3**: 410–411.
21. Kelman GR, Swapp GH, Smith I, Benzie RJ, Gordon NLM. Cardiac output and arterial blood-gas tension during laparoscopy. *British Journal of Anaesthesia* 1972; **44**: 1155–1162.
22. Liu SY, Leighton T, Davis I, Klein S, Lippman M, Bongard F. Prospective analysis of cardiopulmonary responses to laparoscopic cholecystectomy. *Journal of Laparoendoscopic Surgery* 1991; **1**: 241–246.
23. Wittgen CM, Andrus CH, Fitzgerald SD, Baudendistel LJ, Dahms TE, Kaminski DL. Analysis of the hemodynamic and ventilatory effects of laparoscopic cholecystectomy. *Archives of Surgery* 1991; **126**: 997–1001.
24. Rasmussen JP, Dauchot PJ, De Palma RG, Sorensen B, Regula G, Anton AH, Gravenstein JS. Cardiac function and hypercarbia. *Archives of Surgery* 1978; **113**: 1196–1200.
25. Rutten AJ, Ilsley AH, Skrowronski GA, Runciman WB. A comparative study of the measurement of mean arterial blood pressure using automatic oscillometers, arterial cannulation and auscultation. *Anaesthesia and Intensive Care* 1986; **14**: 58–65.
26. Ramsey M III. Noninvasive automatic determination of mean arterial pressure. *Medical & Biological Engineering & Computing* 1979; **17**: 11–14.
27. Yamanaka MK, Sue DY. Comparison of arterial-end-tidal $P\text{CO}_2$ difference and deadspace/tidal volume ratio in respiratory failure. *Chest* 1987; **92**: 832–835.
28. Clements F, Harpole D, Quill T, Jones R, McCann R. Estimation of left ventricular volume and ejection fraction by two-dimensional transoesophageal echocardiography: Comparison of short axis imaging and simultaneous radionuclide angiography. *British Journal of Anaesthesia* 1990; **64**: 331–336.
29. Urbanowicz J, Shaaban J, Cohen N, Cahalan M, Botvinick E, Chatterjee K, Schiller N, Doe M, Matthay M. Comparison of transesophageal echocardiographic and scintigraphic estimates of left ventricular end-diastolic volume index and ejection fraction in patients following coronary artery bypass grafting. *Anesthesiology* 1990; **72**: 607–612.
30. Reichek N, Wilson J, Sutton M, Plappert TA, Goldberg S, Hisshfeld JW. Noninvasive determination of left ventricular end-systolic stress: validation of the method and initial application. *Circulation* 1982; **65**: 99–108.

British Journal of Anaesthesia 1993; 70: 626–630

EFFICACY OF POSTOPERATIVE PAIN TREATMENT REGIMENS USING BOTH BUPRENORPHINE AND PAPAVERETUM SEQUENTIALLY AFTER ABDOMINAL HYSTERECTOMY

D. W. GREEN, L. O'CONNOR AND M. HANNA

SUMMARY

We have undertaken a double-blind, controlled study to test the hypothesis that the efficacy of standard postoperative analgesia by papaveretum or buprenorphine is not compromised by previous or subsequent standard doses of the other agent. After total abdominal hysterectomy under a standardized general anaesthetic, 120 patients (four groups of 30) were allocated randomly to receive, on demand, a single i.v. dose of buprenorphine 0.15 mg or papaveretum 10 mg, followed sequentially by a single dose of i.m. buprenorphine 0.3 mg or papaveretum 20 mg. Three hours after the i.m. dose, all patients received sublingual buprenorphine 0.4 mg. Pain was scored using both a 10-cm horizontal visual analogue scale (VAS) and a nominal scale. Pain intensity differences and patient and nurse satisfaction with the regimens were recorded. Observations were continued for 8 h after operation. The efficacy of papaveretum or buprenorphine was not compromised by previous or subsequent standard doses of the other agent. All four treatment regimens were similarly well tolerated and gave acceptable analgesia in the immediate postoperative period. (Br. J. Anaesth. 1993; **70**: 626–630)

KEY WORDS

Analgesics: buprenorphine, papaveretum. Analgesia: postoperative.

Buprenorphine is a semi-synthetic partial agonist with high affinity at the mu opioid receptor. It is at least 30 times more potent than morphine on a weight-for-weight basis when given by the parenteral route [1]. Although buprenorphine has been shown to be an effective and long acting analgesic by a variety of routes [2–5], its partial agonist profile has led to confusion concerning its use in the postoperative period when it follows, or is followed by, other opioid analgesics [6]. There thus remains the possibility of altered analgesic efficacy if buprenorphine and other mu agonist analgesics, such as papaveretum, are used sequentially in the immediate postoperative period.

The purpose of this study was to test the hypothesis that the efficacy of standard postoperative analgesia by papaveretum or buprenorphine is not compromised by previous or subsequent standard doses of the other agent.

PATIENTS AND METHODS

The study was conducted as a double-blind, parallel group, comparative study of four separate pain treatment regimens based upon the use of both papaveretum (which is the routine in this hospital) and buprenorphine. A research nurse was employed to recruit patients, co-ordinate the study and collect patient data, but was blinded to the individual medication regimen (table I).

We studied 120 female patients aged 18–65 yr and requiring analgesia to alleviate moderate to severe pain after abdominal hysterectomy. Patients were in the weight range 50–90 kg and ASA class I or II. Patients with a history of opioid addiction, current chronic pain management with opioid analgesics for more than 4 weeks, or those who had used opioid analgesics within the previous 7 days were excluded. The study was approved by the local Ethics Committee and conducted in accordance with the Declaration of Helsinki. All subjects gave written, informed consent.

Patients were premedicated with temazepam 20 mg orally, 1 h before the procedure. Anaesthesia was induced with fentanyl 3 $\mu g\ kg^{-1}$ i.v. and propofol 2–3 $mg\ kg^{-1}$ and neuromuscular block produced with vecuronium 0.08 $mg\ kg^{-1}$. The patient's lungs were ventilated with nitrous oxide and 0.5–1 % isoflurane in oxygen and the trachea intubated using a cuffed tracheal tube. During the procedure the lungs were ventilated mechanically and end-tidal carbon dioxide maintained at 4–5 %. Isoflurane 0.5–1 % (end-tidal) was given as required to produce adequate anaesthesia. No further analgesics were given during anaesthesia. Arterial pressure, heart rate and Sp_{O_2} were monitored at 3-min intervals throughout the procedure. After antagonism of residual neuromuscular block with glycopyrronium 5–10 $\mu g\ kg^{-1}$ and neostigmine 20–40 $\mu g\ kg^{-1}$ and return of adequate spontaneous ventilation, the trachea was extubated and the patient returned to the recovery room.

In the immediate postoperative period, when the patient first complained of moderate to severe pain, the first treatment dose was given i.v. The effects of

---

D. W. GREEN, M.B., F.R.C.ANAES.; LYNN O'CONNOR, R.G.N.; M. HANNA, M.B., F.R.C.ANAES.; Department of Anaesthesia, Intensive Care and Pain Relief, King's College Hospital, Denmark Hill, London SE5 9RS. Accepted for Publication: December 17, 1992.

TABLE I. *Postoperative dose of drugs used in the four regimens*

Group	1st (i.v.)	2nd (i.m.)	3rd (s.l.)
1(a)	Buprenorphine 0.15 mg	Papaveretum 20 mg	Buprenorphine 0.4 mg
1(b)	Papaveretum 10 mg	Papaveretum 20 mg	Buprenorphine 0.4 mg
2(a)	Papaveretum 10 mg	Buprenorphine 0.3 mg	Buprenorphine 0.4 mg
2(b)	Buprenorphine 0.15 mg	Buprenorphine 0.3 mg	Buprenorphine 0.4 mg

the i.v. dose were assessed (see later) at 30-min intervals until the patient requested further analgesia. The second treatment was given on the ward, i.m. on demand and assessment continued for 3 h, at which time the third (sublingual) dose was given. The effects of the sublingual dose were assessed hourly for 4 h or until additional analgesics were required (see below).

No other analgesics, including non-steroidal anti-inflammatory drugs, were administered during the study. If a patient's pain was inadequately controlled by the study medication, she was withdrawn from the study and given suitable alternative treatment.

Prochlorperazine 12.5 mg i.m. was given prophylactically with the second i.m. analgesic dose on the ward, according to our usual practice.

Each individual patient treatment was presented as two sublingual tablets in a polythene bag, with the two ampoules (for i.v. and i.m. injection). The treatments were randomized in numerical order in blocks of four—with one of each treatment regimen per block. The randomization code and all information relating to the drug materials were retained in the hospital pharmacy.

Buprenorphine (Reckitt and Colman) was supplied as ampoules containing 0.3 mg in 1 ml and as 0.2-mg sublingual tablets. Papaveretum (C.P. Pharmaceuticals) was supplied as ampoules containing papaveretum 20 mg in 1 ml. Ampoules for i.v. or i.m. injection were identical.

Patients were assessed by the research nurse for pain intensity using a horizontal, 10-cm visual analogue scale (VAS) [7] where one end of the line represents "no pain" (scoring 0) and the other "worst imaginable pain" (scoring 10). A four-point nominal scale was also used: 0 = no pain; 1 = mild pain; 2 = moderate pain; 3 = severe pain [8]. In addition, patients were assessed for pain relief using the following five-point nominal rating scale: no relief = 0; slight relief = 1; moderate relief = 2; good relief = 3; complete relief = 4. At the end of the study, both the patient's and the nurse's overall impression of the drug regimen was assessed using a five-point nominal scale: very poor = 0; poor = 1; moderate = 2; good = 3; very good = 4. Adverse effects were recorded for the duration of the study period.

Statistical analysis

Age, height and weight were compared between treatment groups using analysis of variance with treatment effects in the model. Compliance with the assumptions was checked by diagnostic residual plots. The patient's race, type of incision used, deviations from standard anaesthesia and any pre-study therapy were compared between treatment groups using Fisher's exact test.

From the pain intensity VAS, the pain intensity difference (PID) was calculated for each patient after the i.m. injection. The VAS assessments of pain intensity at each time within each treatment period were analysed using analysis of variance as above. Pain intensity and pain relief ratings were analysed using extended Mantel–Haenszel tests [9]. For both pain variables, pairwise comparisons were made between treatment groups as appropriate in each treatment period. The number of patients who experienced adverse events in each treatment period were compared using Fisher's exact test. Based on previous estimates of VAS pain scores for sublingual buprenorphine used in postoperative pain, a standard deviation of 3.776 (mean = 4.02) gives a group size of 30 patients (i.e. 120 patients in total) which is sufficient to detect a 30% difference in treatment response at the 5% level of significance with 80% power.

RESULTS

One hundred and twenty patients completed the study. All four groups were comparable in age, height and weight (table II).

Treatment groups 1(a) and 2(b) received buprenorphine and their pain scores were similar, as were those of groups 1(b) and 2(a), who received papaveretum. There were no significant differences between the pain scores (VAS and nominal) on the two treatments (figs 1, 2).

There were no significant differences between groups 2(a) and 2(b), indicating that the effect of i.m. buprenorphine was not dependent on whether or not it was preceded by i.v. buprenorphine or i.v. papaveretum. Similarly, there were no significant differences between groups 1(a) and 1(b), indicating that the effect of i.m. papaveretum did not depend on whether or not it had been preceded by i.v. buprenorphine or i.v. papaveretum (figs 1, 2).

There were no significant differences between i.m. buprenorphine and i.m. papaveretum when they

TABLE II. *Patient data (mean (range or* SEM*)). Groups are specified in table I. No significant differences between the groups*

	Treatment group				
	1(a) ($n = 29$)	1(b) ($n = 33$)	2(a) ($n = 30$)	2(b) ($n = 28$)	Total ($n = 120$)
Age (yr)	44.9 (30–65)	44.8 (35–59)	44.2 (29–62)	43.2 (30–51)	44.3 (29–65)
Height (cm)	160.7 (1.3)	159.6 (1.2)	159.6 (1.0)	161.3 (1.0)	160.2 (0.6)
Weight (kg)	65.6 (2.3)	63.8 (1.9)	64.5 (2.1)	66.0 (1.5)	64.9 (1.0)

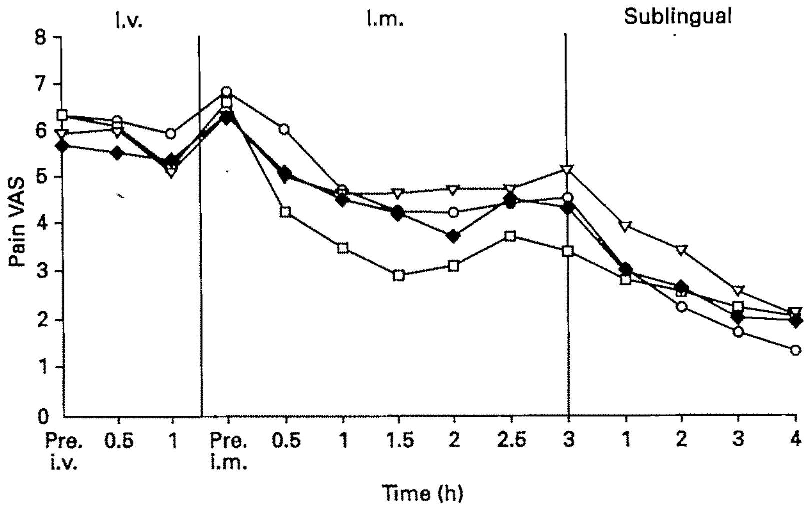


FIG. 1. Visual analogue (VAS) pain scores for the four treatment groups during the three phases, i.v., i.m. and sublingual. □ = B–P–B: group 1(a); ◆ = P–P–B: group 1(b); ○ = P–B–B: group 2(a); ▽ = B–B–B: group 2(b).

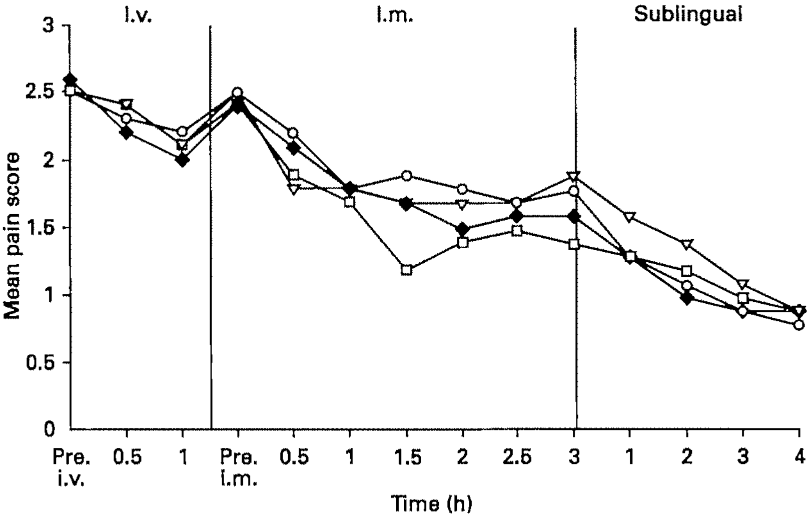


FIG. 2. Nominal pain scores for the four treatment groups during the three phases, i.v., i.m. and sublingual. □ = B–P–B: group 1(a); ◆ = P–P–B: group 1(b); ○ = P–B–B: group 2(a); ▽ = B–B–B: group 2(b).

TABLE III. P *values of comparative pain intensity scores (VAS and nominal) and pain relief in the i.m. phase.* *P < *0.05*

Time after i.m. injection (h)	Pain intensity scores following i.v. buprenorphine. Papaveretum (group 1(a)) *vs* buprenorphine (2(b))	Pain intensity scores following i.v. buprenorphine *vs.* i.v. papaveretum. Groups 1(a) and 2(b) *vs* groups 1(b) and 2(a)	Pain relief following i.v. buprenorphine. Papaveretum (group 1(a)) *vs.* buprenorphine (2(b))
Before	0.52	0.67	—
0.5	0.29	0.03*	0.38
1	0.13	0.69	0.14
1.5	0.02*	0.03*	0.03*
2	0.02*	0.58	0.03*
3	0.02*	0.65	0.01*

followed i.v. papaveretum (groups 1(b) and 2(a)), but when they followed i.v. buprenorphine (groups 1(a) and 2(b)), VAS with i.m. papaveretum were significantly smaller ($P < 0.05$) than those with buprenorphine at 1.5, 2 and 3 h after administration (table III).

Patients who had received i.v. buprenorphine had significantly smaller nominal rating scores with i.m. treatment at 30 min and 1.5 h after dose than those who had received i.v. papaveretum (table III).

PID (relief) was recorded in the i.m. treatment phase. For those patients who had previously received i.v. buprenorphine, pain relief from i.m. papaveretum was significantly greater than that from i.m. buprenorphine at 1.5, 2 and 3 h after administration (table III).

All patients received sublingual buprenorphine 3 h after the i.m. injection, so all comparisons are of the effects of the preceding treatments on the sublingual pain scores.

The pre-sublingual pain scores of patients who had received i.m. papaveretum after buprenorphine i.v. were significantly smaller than those of patients who had received i.m. buprenorphine. However, at all subsequent assessment times there were no significant differences between mean pain scores recorded for the four groups.

Both the patients' and nurse's overall assessment of the four treatment groups were similar. The majority (74%) of the patients assessed the study regimens as "good" or "very good". The majority of the nurse assessments were between "moderate" and "good".

There were no serious adverse events (clinically significant respiratory depression or sedation) in any patient during any limb of the study. Eleven patients withdrew before the end of the study period because of insufficient analgesia. There was no significant difference between the numbers of patients withdrawing from each group.

In the i.v. phase, 19 patients (31%) receiving buprenorphine reported 21 adverse events, while 15 patients (23%) receiving papaveretum reported 18 adverse events. These were mainly nausea, vomiting, or both, for both groups, but four patients in the papaveretum group had a cardiovascular event (hypotension or bradycardia). These differences were not statistically significant.

In the i.m. dose phase, five patients (8%) receiving buprenorphine reported six adverse events while 14 patients (22%) receiving papaveretum reported 15 events. Again, these were mostly nausea, vomiting, or both. In the i.m. treatment phase, significantly more patients receiving papaveretum reported an adverse event ($P < 0.005$).

In the sublingual dose phase, 25 patients (20%) reported 31 adverse events.

DISCUSSION

We have shown that the immediate analgesic effect of i.m. papaveretum did not depend on whether or not it had been preceded by i.v. buprenorphine or i.v. papaveretum. Similarly, the immediate effect of i.m. buprenorphine did not depend on whether or not it had been preceded by i.v. papaveretum or i.v. buprenorphine.

The analgesia was similar with both i.m. buprenorphine and i.m. papaveretum after i.v. papaveretum. Those patients transferred to i.m. papaveretum after i.v. buprenorphine had significantly smaller pain scores at 1.5, 2.5 and 3 h after administration than those transferred to i.m. buprenorphine. This is evidence in favour of an additive effect between a partial and a full opioid agonist. Although this effect was not seen in reverse when buprenorphine i.m. followed papaveretum i.v., a previous study showed improved analgesia when sublingual buprenorphine followed intraoperative morphine i.v. [3].

When administered after i.v. buprenorphine, both i.m. buprenorphine and i.m. papaveretum were associated with significantly smaller nominal rating scores at 30 min and 1.5 h than after i.v. papaveretum. This supports the finding that the analgesic effect of papaveretum is not compromised by previous doses of buprenorphine. It may also indicate that the effective analgesia of i.v. buprenorphine is maintained, and possibly added to, on administration of both i.m. treatments.

Buprenorphine has been studied extensively for postoperative analgesia, on its own [4] or in comparison with papaveretum [2], morphine [3], pethidine [5] and pentazocine [10]. It has been shown to be as effective, usually longer acting, and to have side effects similar to those of the other analgesics studied. Effectiveness by the sublingual route, lack of effect on the sphincter of Oddi [11] and minimal controlled drug status [12] confer additional benefits [7].

The analgesic profile of buprenorphine cannot be explained simply by its pharmacokinetics or partial agonist classification. Although the pharmacokinetics of buprenorphine are similar to those of fentanyl, its onset of action is much slower and its duration of action much longer. This difference can be explained by its greater receptor affinity: Boas and Villiger [13] demonstrated 50% receptor dissociation at 1 h for buprenorphine, compared with 100% at 10 min with fentanyl.

Although buprenorphine has been used successfully for sequential analgesia following high-dose fentanyl–sufentanil anaesthesia [14], some have advised against the use of a partial mu opioid agonist in conjunction with a full opioid agonist, either during operation or in the immediate postoperative period [6]. There are three reasons for this concern.

First, there could be displacement of previously administered opioid agonist by the partial agonist, resulting in reduced analgesia. In practice, a high affinity partial agonist, such as buprenorphine, is likely to antagonize the effects of prior administration of agonist only if the latter has been given in excess and is causing severe respiratory depression. In these circumstances, buprenorphine reverses the respiratory depression in a manner similar to naloxone, although analgesia is maintained better with buprenorphine [15].

Second, the effects of a partial agonist given after a full agonist could be additive. Although this may result in enhanced analgesia, it may also cause respiratory depression. In practice, an additive effect of a partial agonist after a full agonist occurs only when the latter is given in moderate dosage, or when the full agonist is exerting a less than optimal analgesic effect. In such circumstances, the effect on analgesia is beneficial [3] and respiratory depression is unlikely to be severe.

Third, if buprenorphine has been used as the primary analgesic, there is concern that it could render subsequent doses of a full agonist less effective because of its extensive mu receptor binding potential and avidity, and its ability to displace the full agonist [13].

In the present study, however, the efficacy of postoperative analgesia with papaveretum or buprenorphine was not compromised by previous or subsequent standard doses of the other agent. All four treatment regimens were similarly well tolerated and gave acceptable analgesia in the postoperative period.

ACKNOWLEDGEMENTS

This study was supported financially by Reckitt and Colman, Hull, U.K.

REFERENCES

1. Cowan A, Lewis JW, Macfarlane IR. Agonist and antagonist properties of buprenorphine, a new antinociceptive agent. *British Journal of Pharmacology* 1977; **60**: 537–545.
2. Fry ENS. Relief of pain after surgery. A comparison of sublingual buprenorphine and intramuscular papaveretum. *Anaesthesia* 1979; **34**: 549–551.
3. Green DW, Sinclair JR, Mikhael MS. Buprenorphine versus morphine. A comparison of intraoperative and postoperative analgesia. *Anaesthesia* 1985; **40**: 371–375.
4. Harcus AH, Ward AE, Smith DW. Buprenorphine in postoperative pain: results in 7500 patients. *Anaesthesia* 1980; **35**: 382–386.
5. Harmer M, Slattery PJ, Rosen M, Vickers MD. Intramuscular on demand analgesia: double blind controlled trial of pethidine, buprenorphine, morphine and meptazinol. *British Medical Journal* 1983; **286**: 680–682.
6. Sublingual buprenorphine. *Drugs and Therapeutic Bulletin* 1982; **20**: 74–76.
7. Revill SI, Robinson JO, Rosen M, Hogg MIJ. The reliability of a linear analogue for evaluating pain. *Anaesthesia* 1976; **31**: 1191–1198.
8. Huskisson EC. Measurement of pain. *Lancet* 1974; **2**: 1127–1128.
9. Landis RJ, Heyman ER, Koch GC. Average partial association in three-way contingency tables: A review and discussion of alternative tests. *International Statistical Review* 1973; **46**: 237–254.
10. Harmer M, Slattery PJ, Rosen M, Vickers MD. Comparison between buprenorphine and pentazocine given i.v. on demand in the control of postoperative pain. *British Journal of Anaesthesia* 1983; **55**: 21–24.
11. Cuer JC, Dapoigny M, Ajmi S. Effects of buprenorphine on motor activity of the sphincter of Oddi in man. *European Journal of Clinical Pharmacology* 1989; **36**: 203–204.
12. World Health Organisation. *Twenty-Fifth Report of the WHO Expert Committee on Drug Dependence*. Geneva: WHO, 1989.
13. Boas RA, Villiger JW. Clinical actions of fentanyl and buprenorphine. The significance of receptor binding. *British Journal of Anaesthesia* 1985; **57**: 192–196.
14. De Castro J, Parmentier P. Buprenorphine in analgesic anaesthesia. *Proceedings of the VI Congress of Anaesthesiology, Mexico City* 1976; Section **5**: 3.
15. Boysen K, Hertel S, Chraemmer-Jorgensen B, Risbo A, Poulsen NJ. Buprenorphine antagonism of respiratory depression following fentanyl anaesthesia. *Acta Anaesthesiologica Scandinavica* 1988; **32**: 490–497.

British Journal of Anaesthesia 1993; 70: 631–633

EVALUATION OF THE ANALGESIC EFFECT OF METOCLOPRAMIDE AFTER OPIOID-FREE ANALGESIA

B. LISANDER

SUMMARY

Metoclopramide may enhance opioid analgesia, but it is not known if the drug is analgesic itself. This question was examined in a double-blind, randomized study of 38 patients undergoing knee arthroscopy with opioid-free anaesthesia comprising propofol, isoflurane and nitrous oxide in oxygen. At the end of surgery, patients received either metoclopramide 0.5 mg kg^{-1} or placebo i.v. After operation, they received patient-controlled analgesia with pethidine for 3 h, during which period, pain score was assessed on a visual analogue scale (VAS). There were no significant differences between the groups in the patterns of pethidine consumption. However, the VAS-pain scores tended to be smaller in the metoclopramide group; this difference was significant 30 min after operation. These results do not demonstrate conclusively a clinically relevant analgesic action of metoclopramide. (Br. J. Anaesth. **1993**; **70**: 631–633)

KEY WORDS

Analgesia: postoperative, patient-controlled. Analgesics: metoclopramide.

Clinical studies have reported an analgesic effect of metoclopramide in ureterolithiasis [1], labour [2], termination of pregnancy [3] and prosthetic hip surgery [4]. The mechanisms by which the drug exerts its analgesic action are unknown. In some studies, it enhanced the effect of opioids [2–4]. However, there are reports that metoclopramide is analgesic, even when given alone, in patients [1] and animals [5, 6].

The aim of the present study was to examine if metoclopramide is analgesic by itself in the postoperative situation. The degree of postoperative pain in a study of this type is important: it should not be so severe as to make the majority of patients require supplementary opioid analgesics from the outset, as this would focus the study on the interactive effects of opioids and metoclopramide. Patients undergoing arthroscopy of the knee were considered suitable for this purpose, and no opioids were given during surgery.

PATIENTS AND METHODS

The study was performed in 38 patients undergoing unilateral arthroscopy of the knee in a double-blind, randomized design. Patients with a history of cardiac decompensation, coronary insufficiency, extrapyramidal symptoms, hepatic or gastrointestinal disease or increased serum concentrations of creatinine were excluded. The study was approved by the local Ethics Committee and informed consent was obtained from the patients, all of whom were in ASA group I or II. Before operation, they were instructed about postoperative estimation of pain and the use of patient-controlled analgesia. Triazolam 0.25 mg was given by mouth as premedication 1 h before anaesthesia. Atropine 0.5 mg i.v. was given and general anaesthesia induced with propofol in a dose sufficient to obtund the eyelash reflex. Anaesthesia was maintained with isoflurane and nitrous oxide in oxygen, by spontaneous ventilation via a face mask. The arthroscopies were either diagnostic or were performed for the purpose of partial meniscectomy.

At the end of surgery metoclopramide 0.5 mg kg^{-1} i.v. or placebo was given from coded ampoules containing metoclopramide 100 mg ml^{-1} (Primperan, Lundbeck). The appropriate dose was diluted with 20 ml of saline before use.

After operation, patients were transferred to the postoperative ward. When they could repeat instructions concerning the patient-controlled analgesia (PCA), they were connected to a PCA pump (Prominject Pharmacia) which delivered 10-mg bolus doses of pethidine 10 mg ml^{-1} with a lock-out time of 5 min. After 3 h, the PCA treatment was terminated.

Pain scores were assessed on a visual analogue scale (VAS) (0 mm = no pain; 100 mm = worst pain imaginable) every 30 min during the PCA treatment, starting at 30 min.

Data are presented as median (25–75% range). Statistical analysis was performed with the Mann–Whitney rank sum test or Fisher's exact test. Correction for multiple comparisons (VAS pain scores) was made [7]. $P < 0.05$ was considered statistically significant. For power analysis, a formula for dichotomous values [8] was used.

RESULTS

Nineteen patients received metoclopramide 0.5 mg kg^{-1} i.v. and 19 placebo (control group) (table I).

There were no significant differences between

Björn Lisander, M.D., Ph.D., Department of Anaesthesiology, Linköping University Hospital, S-581 85 Linköping, Sweden.
Accepted for Publication: January 21, 1993.

TABLE I. *Patient data (median (25–75% range)). Wake-up time = time between end of surgery and start of PCA*

	Metoclopramide (n = 19)	Placebo (n = 19)
Age (yr)	27 (23–37)	34 (23–49)
Sex (M/F)	17/2	14/5
Weight (kg)	75 (66–84)	80 (63–85)
Preoperative VAS pain score (mm)	0 (0–0)	0 (0–0)
Meniscectomy (No. patients)	9	11
Duration of surgery (min)	20 (15–35)	25 (20–40)
Wake-up time (min)	11 (9–14)	11 (9–15)

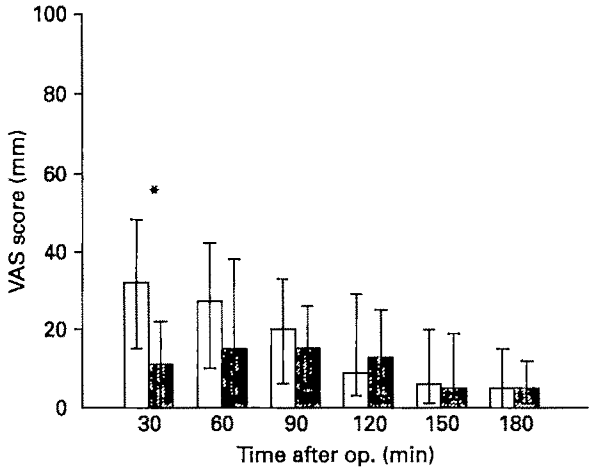


FIG. 1. Postoperative VAS pain scores (median, 25–75% range). □: Placebo (n = 19); ▨: metoclopramide (n = 19). * Significant difference ($P < 0.05$) between groups; at that time, three placebo and five metoclopramide patients had taken PCA pethidine: the difference remained significant after exclusion of these patients.

groups in administration of PCA pethidine. The total dose was 10 (0–10) mg in the metoclopramide group and 10 (0–20) mg in the control group; time to the first dose was 167 (29–∞) min in the metoclopramide group and 70 (45–∞) min in the control group. In the control group, 63% of patients (12 of 19) received PCA pethidine. The study has a power of 80% to detect a decrease in this percentage to 20%. In the metoclopramide group, 53% of patients (10 of 19) received PCA pethidine. Eight patients in the placebo group and three in the metoclopramide group required more than one dose of pethidine.

VAS pain scores (fig. 1) tended to be smaller in the metoclopramide group (significant at 30 min of PCA treatment). Time from the end of surgery (when the study drugs were given) to start of the PCA treatment (when the patients could repeat instructions) was used as a measure of recovery time; no significant difference was noted between groups (table I). Patients receiving metoclopramide were not notably drowsy. No side effects attributable to metoclopramide such as extrapyramidal disturbances, were observed, and emesis was observed in only one patient (receiving placebo and no pethidine).

DISCUSSION

Metoclopramide is a structural analogue of procaine amide, but lacks local anaesthetic and antiarrhythmic activity [9]. Analgesic properties of metoclopramide have been demonstrated in animal experiments and calcium channel- [5], opioid- [5] or prolactin- [6] mediated mechanisms have been suggested.

Clinical studies also have reported analgesic effects of the drug. I.v. metoclopramide 20 mg was at least as effective as atropine 0.5 mg plus morphine 20 mg s.c. in relieving acute pain in ureterolithiasis [1]. I.m. metoclopramide 10 mg enhanced the analgesic effect of pethidine in labour [2]; the same dose i.v. decreased the need for morphine in termination of pregnancy [3]. In all these studies, the analgesic effects were interpreted as mediated by an action of metoclopramide on painful contractions of smooth muscle. However, in a recent study [4] in which patients underwent total hip replacement under intrathecal analgesia supplemented with intrathecal morphine, metoclopramide 1 mg kg^{-1} i.v. followed by an infusion of 1.5 mg kg^{-1} over 9 h decreased the need for postoperative analgesics and prolonged the pain-free time. This suggests that metoclopramide may exert a true analgesic action in the clinical setting.

The mechanism of metoclopramide analgesia remains unknown. The drug antagonizes the 5-hydroxy tryptamine 3 ($5HT_3$) receptor, which is probably the major mechanism of the anti-emetic effect of "high-dose" metoclopramide [10]. Although $5HT_3$ receptor block may be associated with analgesia [11], clinical administration of ondansetron was not shown to decrease the need for postoperative analgesics [12].

Metoclopramide is a potent antagonist of the dopaminergic D_2 receptor [13], accounting for the extrapyramidal side effects of the drug and probably also for its low-dose, anti-emetic effect [10]. Some researchers have suggested that dopaminergic *agonists* increase the efficacy of morphine analgesia, while others have reported an antagonism. These conflicting results may reflect differing degrees of activation of the D_1 and D_2 receptor subtypes [14, 15] or of presynaptic autoreceptors and postsynaptic receptors [16]. While the effects of dopaminergic agonists and antagonists on pain processing are thus insufficiently known, they have frequently been described in terms of enhancement or antagonism of opioid-induced analgesia. There is increasing evidence that such an interaction reflects a functional interconnection between opioid and dopaminergic mechanisms [15].

Even though the D_2-antagonist metoclopramide may enhance opioid analgesia [2–4], analgesic effects of metoclopramide, given alone, have been reported in man [1] and in animals [5, 6]. However, this does not exclude an interaction of the drug with *endogenous* opioid mechanisms.

The aim of the present study was to see if metoclopramide has an analgesic effect in the absence of exogenous opioids. Postoperative PCA consumption of pethidine was chosen as an indicator of an analgesic effect in the expectation that the time to the first dose and the number of patients receiving pethidine after operation would give information on the analgesic properties of metoclopramide *per se*. This was the main objective of the study and it should be noted that the magnitude of the PCA bolus dose and the number of doses after the first one were unimportant in this context. After receiving a first dose of PCA pethidine, the patient could furnish no further information concerning the effect of metoclopramide alone: the number of patients taking more than one dose and the cumulated number of doses in each of these patients describe the interactive effects of metoclopramide and pethidine—a problem for which the study was not designed and regarding which conclusions are not justified. We found no significant differences in postoperative pethidine requirement between patients who received metoclopramide 0.5 mg kg^{-1} and those who received placebo.

The VAS pain scores in figure 1 include observations in patients who had taken PCA pethidine and should therefore be interpreted with caution. However, a trend was observed towards smaller VAS pain scores in the metoclopramide group and this attained statistical significance 30 min after operation, indicating that identical analgesia was not achieved with the PCA treatment. It is now believed commonly that measurement of pain can be accomplished by assessing drug intake during PCA. However, patients utilizing PCA usually do not achieve total analgesia, some fail to obtain adequate relief of pain and significant differences in pain scores have been demonstrated between supposedly comparable groups of patients utilizing PCA [17]. Actual estimations of pain must therefore be accorded due significance. After operation, patients may refrain from utilizing PCA for a variety of reasons, particularly if their pain is tolerable.

There are several possible mechanisms which would explain why the VAS pain scores were markedly less in the metoclopramide group early in the postoperative course but not later. Elimination of metoclopramide is unlikely to have been the cause, as the drug has a terminal half-life of 4.5–8.8 h [18]. The drug may have delayed elimination of the anaesthetic agents and hence depressed nociceptive neurotransmission [19] for example as a result of decreased ventilation; however, the time from the end of surgery to the start of PCA was similar in both groups. More sophisticated measures of recovery are needed before definite conclusions can be drawn in this respect. Even if the rate of elimination of the anaesthetic agents is assumed to have been the same in both groups, metoclopramide may have interacted with residual anaesthetic agents to cause analgesia: common mechanisms of action may exist. For example, changes in neuronal fluxes of the calcium ion are important in producing general anaesthesia and calcium channel antagonists have been reported to increase the potency of drugs such as nitrous oxide, volatile anaesthetics, barbiturates, benzodiazepines and opioids [20, 21]. Metoclopramide analgesia, also, can be potentiated by the calcium channel blocker nifedipine and counteracted by calcium chloride [5].

REFERENCES

1. Müller TF, Naesh O, Svare E, Jensen A, Glyngdal P. Metoclopramide (Primperan®) in the treatment of ureterolithiasis. A prospective double-blind study of metoclopramide compared with morphatropin on ureteral colic. *Urologia Internationalis* 1990; 45: 112–113.
2. Vella L, Francis D, Houlton P, Reynolds F. Comparison of the antiemetics metoclopramide and promethazine in labour. *British Medical Journal* 1985; 290: 1173–1175.
3. Rosenblatt WH, Cioffi AM, Sinatra R, Saberski LR, Silverman DG. Metoclopramide: An analgesic adjunct to patient controlled analgesia. *Anesthesia and Analgesia* 1991; 73: 553–555.
4. Kandler D, Lisander B. Analgesic action of metoclopramide in prosthetic hip surgery. *Acta Anaesthesiologica Scandinavica* 1993; 37: 49–53.
5. Ramaswamy S, Lenin Kamatchi G, Bapna JS. Involvement of calcium in metoclopramide analgesia. *IRCS Journal of Medical Science* 1986; 14: 769.
6. Ramaswamy S, Bapna JS. Analgesic effect of metoclopramide and its mechanism. *Life Sciences* 1986; 38: 1289–1292.
7. Glantz SA. *Primer of Biostatistics*, 2nd Edn. New York: McGraw-Hill Book Company, 1987; 345.
8. Young MJ, Bresnitz EA, Strom BL. Sample size nomograms for interpreting negative clinical studies. *Annals of Internal Medicine* 1983; 99:248–251.
9. Harrington RA, Hamilton CW, Brogden RN, Linkewich JA, Romankiewicz JA, Heel RC. Metoclopramide. An updated review of its pharmacological properties and clinical use *Drugs* 1983; 25: 451–494.
10. Andrews PLR, Hawthorn J. The neurophysiology of vomiting. *Baillière's Clinical Gastroenterology* 1988; 2: 141–168.
11. Zemlan FP, Behbehani MM, Murphy RM. Serotonin receptor subtypes and the modulation of pain transmission. *Progress in Brain Research* 1988; 77: 349–355.
12. Leeser J, Lip H. Prevention of postoperative nausea and vomiting using ondansetron, a new, selective $5HT_3$ receptor antagonist. *Anesthesia and Analgesia* 1991; 72: 751–755.
13. LaHoste GJ, Marshall JF. Non-additivity of D_2 receptor proliferation induced by dopamine denervation and chronic selective antagonist administration: evidence from quantitative autoradiography indicates a single mechanism of action. *Brain Research* 1989; 502: 223–232.
14. Zarindast MR, Moghaddampur E. Opposing influences of D-1 and D-2 dopamine receptors activation on morphine-induced antinociception. *Archives Internationales de Pharmcodynamie et de Thérapie* 1989; 300: 37–50.
15. Grip G, Svensson A, Gordh T jr, Post C, Hartvig P. Histopathology and evaluation of potentiation of morphine-induced antinociception by intrathecal droperidol in the rat. *Acta Anaesthesiologica Scandinavica* 1992; 36: 145–152.
16. Strömbom U. Antagonism of halperidol of locomotor depression induced by small doses of apomorphine. *Journal of Neural Transmission* 1977; 40: 191–194.
17. Lehmann KA. Patient-controlled intravenous analgesia for postoperative pain relief. *Advances in Pain Research and Therapy* 1991; 18: 481–506.
18. McGovern EM, Grevel J, Bryson SM. Pharmacokinetics of high-dose metoclopramide in cancer patients. *Clinical Pharmacokinetics* 1986; 11: 415–424.
19. Savola KL, Woodley SJ, Maze M, Kendig JJ. Isoflurane and an α_2-adrenoceptor agonist suppress nociceptive neurotransmission in neonatal rat spinal cord. *Anesthesiology* 1991; 75: 489–498.
20. Dolin SJ, Little JH. Effects of "nitrendipine" on nitrous oxide anesthesia, tolerance and physical dependence. *Anesthesiology* 1989; 70: 91–97.
21. Horváth G, Szikszay M, Benedek G. Potentiated hypnotic action with a combination of fentanyl, a calcium channel blocker and an α_2-agonist in rats. *Acta Anaesthesiologica Scandinavica* 1992; 36: 170–174.

British Journal of Anaesthesia 1993; 70: 634–638

INCREMENTAL SPINAL ANAESTHESIA FOR ELECTIVE CAESAREAN SECTION: MATERNAL AND FETAL HAEMODYNAMIC EFFECTS

S. C. ROBSON, G. SAMSOON, R. J. BOYS, C. RODECK AND B. MORGAN

SUMMARY

We have performed serial haemodynamic investigations in 20 women undergoing elective Caesarean section under continuous spinal anaesthesia with a 32-gauge catheter with 0.5% heavy bupivacaine. Cardiac output was measured by Doppler and cross-sectional echocardiography at the aortic valve. Doppler flow velocity waveforms were recorded also from the umbilical artery. A block to T4 or above was achieved in all patients. The median dose of 0.5% bupivacaine administered was 2.0 ml (range 1.5–4.5 ml). Mean cardiac output increased from 7 to 8 litre min^{-1} after preloading with Ringer lactate solution 1.5 litre and then remained unchanged after injection of bupivacaine. Two subjects developed hypotension, although mean values of arterial pressure and umbilical artery pulsatility index did not change. The median umbilical artery pH was 7.27 (range 6.98–7.32) and there was a significant correlation between pH and the maximum percentage decrease in cardiac output. The results suggest that continuous spinal anaesthesia is associated with greater haemodynamic stability than single bolus spinal injection. (Br. J. Anaesth. 1993; **70**: 634–638)

KEY WORDS

Anaesthesia: obstetric. Anaesthetic techniques: extradural, spinal. Measurement techniques: Doppler ultrasound, echocardiography. Placenta: umbilical artery flow.

Spinal anaesthesia has several advantages in comparison with extradural anaesthesia for elective Caesarean section; the block is faster and more reliable and, because smaller doses of local anaesthetic are used, the risk of toxicity is reduced [1, 2]. However, decreases in arterial pressure and cardiac output are greater with a single subarachnoid injection and these haemodynamic changes have been associated with alterations in Doppler waveform indices in the umbilical artery and a decrease in umbilical arterial pH at delivery [3, 4].

Spinal anaesthesia using a catheter allows incremental injection of local anaesthetic. This produces a more gradual and predictable block which may be associated with a smaller incidence of hypotension [5]. However, changes in arterial pressure do not accurately reflect changes in maternal cardiac output; indeed, we have shown recently that, unlike changes in maternal cardiac output and umbilical artery Doppler flow velocity waveform indices, changes in arterial pressure do not correlate with umbilical arterial pH at delivery [3]. Although several workers have investigated the haemodynamic changes after single injection spinal anaesthesia, comparable studies have not been performed during incremental spinal anaesthesia.

Cardiac output can be calculated from aortic blood velocity, measured by Doppler ultrasound, combined with aortic orifice cross-sectional area, measured by cross-sectional echocardiography. The technique has been validated in pregnancy [6] and allows reproducible, non-invasive measurements of cardiac output [7]. Doppler ultrasound can also be used to assess the fetal umbilical circulation and flow velocity waveform indices have been shown to be superior to cardiotocography in predicting fetal compromise [8]. We have used these techniques to study maternal and fetal haemodynamic changes during incremental subarachnoid injection of bupivacaine for elective Caesarean section.

PATIENTS AND METHODS

We studied 23 healthy women with a singleton pregnancy admitted for elective Caesarean section at term. Three women were excluded subsequently because of failure to insert the subarachnoid catheter. Details of the remaining 20 subjects are shown in table I. The procedure was explained to each subject and written consent was obtained. The study was approved by the local Ethics Committee.

Each subject received oral ranitidine 150 mg on the evening before and on the morning of the operation. Sodium citrate 0.3 mol litre^{-1} (30 ml) was given on arrival of the patient in the operating theatre. After insertion of an i.v. cannula, Ringer lactate solution 1 litre was infused over approximately 15 min immediately before anaesthesia. With the subject in the left lateral position, a 25-gauge spinal needle (Becton Dickinson) was introduced into the subarachnoid space at the L3–4 intervertebral space. A 32-gauge catheter (Microspinal) was then threaded, via the needle, 3 cm into the

---

S. C. ROBSON, M.R.C.O.G.; C. RODECK, F.R.C.O.G.; G. SAMSOON, F.R.C.ANAES.; B. MORGAN, F.R.C.ANAES.; R.P.M.S. Institute of Obstetrics and Gynaecology, Queen Charlotte's and Chelsea Hospital, Goldhawk Road, Chiswick, London. R. J. BOYS, PH.D., B.SC., Department of Statistics, University of Newcastle Upon Tyne, Claremont Road, Newcastle Upon Tyne. Accepted for Publication: January 21, 1993.

TABLE I. *Patient details (mean (range or* SD*)).* †*Macrosomia; previous berry aneurysm*

Age (yr)	33.3 (24–42)
Nulliparous (No.)	7
Height (m)	1.63 (0.06)
Weight (kg)	76.8 (7.7)
Gestation (weeks)	38.8 (1.3)
Indication for Caesarean section	
Previous CS	11
Breech	7
Other	2†
Birthweight of infant (kg)	3.38 (0.37)

subarachnoid space. One millilitre of 0.5% heavy bupivacaine was injected intrathecally with the mother in the left semi-lateral position. Additional injections of 0.5% heavy bupivacaine 0.5–1.0 ml were given after 5 min and repeated every 3–5 min until a bilateral block from T4 to S5 had been achieved. The block was assessed at 2 min, using the absence of perception of cold sensation to an ethyl chloride spray, and this was repeated every 2 min thereafter until the commencement of surgery. An infusion of Ringer lactate solution 1 litre containing ephedrine 60 mg was commenced immediately after injection of the initial dose of bupivacaine. Thereafter, the rate was determined by the anaesthetist according to the arterial pressure.

Arterial pressure was measured using an automatic non-invasive monitor (Marquette). Measurements of systolic, mean and diastolic pressure were obtained every 2 min. Hypotension was defined as a reduction in systolic pressure of > 20% from the baseline, preanaesthetic value, and was treated by increasing the rate of the ephedrine infusion and, if necessary, additional bolus doses of ephedrine 5–10 mg.

Cardiac output was measured using cross-sectional and Doppler echocardiography. The principles and techniques of aortic flow measurement have been described previously [7]. Briefly, aortic blood velocities were recorded using a 2-MHz continuous wave Doppler transducer (Vingmed) placed in the suprasternal notch. A spectrum analyser performed fast Fourier transform analysis of the Doppler signal and the output was converted to velocity according to the Doppler equation. The angulation of the ultrasound beam was adjusted until the highest velocities with the least spectral dispersion were obtained; these were then stored in the computer memory and it was assumed that the recorded velocities were those at the aortic orifice and that the beam was parallel with flow. Heart rate and systolic velocity integral (area under the velocity curve) were calculated automatically by the computer. For the latter, calculations were made using 15/16 of the maximum frequency in order to exclude high frequency artefacts. The average of eight to 10 consecutive cycles was used for each determination. Systolic aortic orifice diameter was measured in the parasternal long axis plane using a 5-MHz cross-sectional transducer (Ausonics). Measurements were made from the leading edge of the anterior wall to the leading edge of the posterior wall. Diameters from five consecutive beats were averaged and cross-sectional area was calculated from $\pi(D/2)^2$, where D = mean aortic orifice diameter. Cardiac output was calculated from the formula: cardiac output (litre min^{-1}) = stroke volume (ml) × heart rate (beat min^{-1}), where stroke volume = velocity integral (cm) × cross-sectional area (cm^2).

Flow velocity waveforms from the umbilical artery were recorded using a 4-MHz continuous wave transducer linked to the same spectral analyser. Pulsatility index was calculated automatically by the computer using 15/16 of the maximum recorded frequency. The average of three consecutive cycles was used for each determination.

Investigations were performed in the operating theatre with the subject in the left semi-lateral (45°) position. Doppler recordings were completed in 2–3 min and cross-sectional echocardiographic recordings in 1–2 min. Echocardiographic measurements were performed before any intervention, after preloading with Ringer's lactate solution 1 litre and at 5-min intervals after the initial injection of bupivacaine until the time of preparation for surgery. Arterial pressure measurements were continued during the echocardiographic measurements and the mean of two consecutive measurements was used for analysis.

The time between the initial spinal injection of bupivacaine and the start of surgery and the time between the uterine incision and delivery were recorded. At the time of delivery, the umbilical cord was double clamped. Umbilical arterial and venous samples were collected and pH and blood-gas analysis performed within 10 min of delivery of the infant (Radiometer ABL-30). One- and 5-min Apgar scores were assigned by the paediatrician. All subjects had an uncomplicated Caesarean section with a median blood loss of 500 ml (range 300–750 ml).

The haemodynamic results from the 20 subjects having incremental spinal anaesthesia were compared with those from 16 women undergoing elective Caesarean section under standard, single-bolus spinal anaesthesia (mean dose 0.5% bupivacaine 2.2 (SD 0.2) ml). The haemodynamic results in the latter group were obtained using exactly the same methodology; data have been reported previously [3].

Statistical analysis

A repeated measures analysis of variance was performed for each variable using the statistical package BMDP. To overcome the problem of multiple significance testing, the differences between time points were compared using the Studentized range at the 1% level:

$$\text{Range} = q_{(v)} \times (s^2/\sqrt{n})$$

where $q_{(v)}$ = critical value for comparing two time points; s^2 = residual mean square with v degrees of freedom; n = number of subjects. Differences between the incremental and standard spinal groups were compared using Student's t test for normally distributed data and the median test for non-normally distributed data. The association between the change in various haemodynamic variables and umbilical artery pH was assessed by Pearson's correlation coefficient.

RESULTS

The median dose of 0.5 % bupivacaine administered was 2.0 ml (range 1.5–4.5 ml); five subjects required more than 2.5 ml (3.0 ml ($n = 3$), 3.5 ml ($n = 1$), 4.5 ml ($n = 1$)). The number of additional doses required to achieve a block to T4 were: one in four subjects, two in 10 subjects, three in one subject, four in four subjects and five in one subject. A block to T4 or above was achieved by 20 min after the initial injection in 15 subjects (75 %). Upper levels of sensory block achieved were: T4 ($n = 15$); T3 ($n = 2$); T2 ($n = 3$).

Details of operations and neonates are shown in table II. Hypotension occurred in two of 20 subjects (10 %). The umbilical artery pH was < 7.2 in two fetuses (7.19 and 6.98), although in both the 1- and 5-min Apgar scores were normal.

Satisfactory Doppler and cross-sectional recordings were obtained in all subjects. The mean results, together with those of arterial pressure are shown in table III. No patient developed hypotension between the completion of the final haemodynamic recordings and delivery. Because of delay in establishing the block, measurements were continued until 20 min in three subjects and 30 min in one subject; cardiac output and umbilical artery pulsatility index remained stable in each. Systolic, diastolic and mean arterial pressure did not change during the study period. Stroke volume and cardiac output increased after preloading and then returned to basal values at 5 min and 10 min, respectively, after the initial dose of bupivacaine. Thereafter there was no further change. Heart rate was increased at 5 min and remained increased. Fetal heart rate was increased at 15 min. No statistically significant changes were observed in umbilical artery pulsatility index.

TABLE II. *Details of operations and neonates (mean (SD) or median (range))*

I.v. fluid (ml)	1373 (156)
Ephedrine (mg)	22.4 (9.4)
Injection–skin incision interval (min)	32.5 (25–53)
Uterine incision–delivery interval (min)	0.9 (0.3)
Umbilical artery	
pH	7.27 (6.98–7.32)
$P\text{CO}_2$ (kPa)	7.2 (1.0)
$P\text{O}_2$ (kPa)	2.0 (0.7)
Base excess (mmol litre^{-1})	−3.5 (−1.7 to −17.3)
Umbilical vein	
pH	7.33 (7.13 to 7.37)
$P\text{CO}_2$	5.7 (0.5)
$P\text{O}_2$	3.5 (0.9)
Base excess (mmol litre^{-1})	−3.0 (−1.1 to −14.2)
Apgar < 7 at 1 min	0
Apgar < 7 at 5 min	0

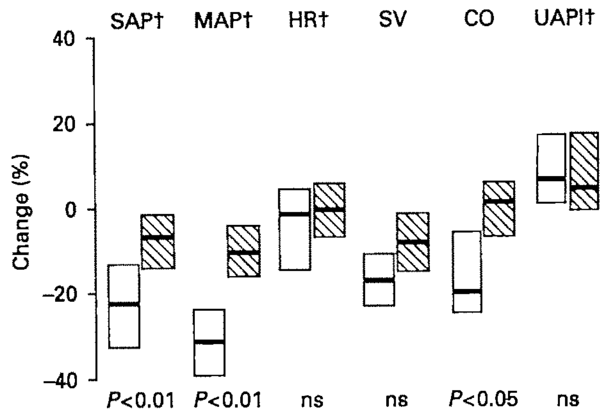


FIG. 1 Maximum percentage change in haemodynamic measurements during incremental spinal anaesthesia for elective Caesarean section ($n = 20$) (▨) compared with those previously reported by the authors using similar methodology during standard spinal anaesthesia ($n = 16$) (☐) (median† or mean and 95 % confidence intervals). Comparison between groups use median test† or Student's t test. For umbilical artery pulsatility index (UAPI), figures are calculated from the maximum percentage increase. For other variables, figures were calculated from the maximum decrease, expressed as a percentage of the baseline value, after injection of bupivacaine. Where there was no decrease, the minimum increase was used in the analysis. SAP = Systolic arterial pressure; MAP = mean arterial pressure; HR = heart rate; SV = stroke volume; CO = cardiac output.

The maximum percentage change in haemodynamic measurements, expressed as a percentage of the baseline value is shown in figure I. Systolic arterial pressure decreased in 16 of 20 subjects, while cardiac output decreased in eight. The largest reduction in cardiac output (24 %) occurred in the

TABLE III. *Haemodynamic data in the spinal catheter group. † Studentized range. Differences between time points greater than SR significant at* P *< 0.01*

			Time after first dose of bupivacaine (min)				
	Basal	After preload	5	10	15	SE	SR†
Arterial pressure (mm Hg)							
Systolic	124.2	127.1	125.1	123.5	123.5	2.3	8.4
Diastolic	77.0	80.1	73.6	74.3	72.7	1.8	6.7
Mean	92.7	95.8	90.6	90.5	89.6	1.8	6.5
Aortic area (cm^2)	3.97	3.94	3.92	3.93	3.94	0.02	0.06
Velocity integral (cm)	21.3	24.1	21.5	20.9	21.2	0.5	1.8
Stroke volume (ml)	84.0	94.8	84.0	81.7	83.1	1.8	6.5
Heart rate (beat min^{-1})	79.9	81.9	89.7	88.4	87.9	1.8	6.8
Cardiac output (litre min^{-1})	6.67	7.76	7.49	7.15	7.17	0.16	0.61
Total peripheral resistance (dyn s^{-1} cm^{-5})							
Fetal heart rate (beat min^{-1})	136.1	140.1	141.7	143.6	149.7	0.0	7.6
Umbilical artery pulsatility index	0.80	0.78	0.80	0.78	0.77	0.02	0.07

subject who subsequently delivered the only acidaemic infant (umbilical artery pH 6.98, base deficit 17.3 mmol litre^{-1}). Interestingly, although the cardiotocograph showed reduced baseline variability after this episode, umbilical artery pulsatility index did not change. Comparative data during standard spinal anaesthesia are shown also in figure 1. The maximum percentage decreases in systolic arterial pressure, mean arterial pressure and cardiac output were greater with the standard spinal technique. There was a significant correlation between umbilical artery pH and the maximum percentage decrease in cardiac output ($r = 0.55$) during incremental spinal anaesthesia, but not with the maximum changes in other haemodynamic measurements.

One subject complained of headache 24 h after operation; she described this as mild, lasting less than 24 h and being relieved by simple analgesics. All the spinal catheters were removed intact. No neurological sequelae were evident in any of the subjects at the time of discharge from hospital.

DISCUSSION

The haemodynamic changes associated with spinal anaesthesia represent the greatest potential hazard of this technique for mother and fetus. The results of the present study show that incremental injection of 0.5% bupivacaine using a spinal microcatheter provided a satisfactory block, with little alteration in maternal arterial pressure and cardiac output. Fetal umbilical arterial flow velocity waveform indices also remained stable during anaesthesia.

Since the completion of this study, reports of cauda equina syndrome associated with the use of small-bore catheters for continuous spinal anaesthesia have led the Food and Drug Administration in the U.S.A. to recall all spinal microcatheters of 27 gauge and smaller [9]. This complication has been reported in 11 patients in whom a small-bore catheter was used to inject 5% lignocaine with 7.5% glucose into the intrathecal space. Because of the potential benefits of continuous spinal anaesthesia and because the potential hazards and means of avoiding them are known, the Department of Health have taken the view that small-bore catheters should continue to be made available for use in the U.K. [10].

Rigler and colleagues [11] reported four cases of cauda equina syndrome in which the dose of local anaesthetic given was greater than that usually administered with a single injection technique. The authors postulated that neurotoxicity resulted from a combination of maldistribution and a relatively large dose of local anaesthetic. Several characteristics of microcatheters may permit maldistribution: the greater resistance reduces the maximum rate of injection and the small size and flexibility may increase the risk of unintentional sacral positioning [11]. Ross, Coda and Heath [12] studied local anaesthetic distribution in a spinal model. They showed that distribution of lignocaine was less uniform and lignocaine concentration in the dependent portions of the model greater after injection through microcatheters compared with a 20-gauge catheter. Wildsmith [13] also drew attention to the possibility of osmotic damage. Although large doses of local anaesthetic have been given during continuous spinal anaesthesia without ill effect [14], it would seem prudent, in view of the probable association with neural damage, to avoid doses far in excess of those given during standard single-injection spinal anaesthesia [15].

Kestin and colleagues [5] compared incremental spinal anaesthesia using a 32-gauge catheter with extradural anaesthesia in women undergoing elective Caesarean section. The spinal catheter was quicker to place and spinal anaesthesia was quicker to establish compared with the extradural technique. Haemodynamic stability and the quality of the block were similar in the two groups. As no previous study had compared haemodynamic changes during continuous and single injection spinal anaesthesia for Caesarean section, we compared the present results with those from 16 previously reported women given a single bolus of 0.5% bupivacaine [3]. Both groups received the same preload and ephedrine regimen and both had identical measurements performed at the same time points. We therefore felt this was an appropriate comparison. Single bolus injection of bupivacaine was associated with greater reductions in arterial pressure and cardiac output. The incidence of hypotension (decrease in systolic pressure > 20%) was also greater in the single bolus group (11 of 16 compared with two of 20 ($P < 0.01$)). These changes were associated with a tendency towards improved umbilical arterial acid–base values in the incremental group (median pH 7.27 (range 6.98–7.32) compared with 7.23 (7.02–7.32) ($P = 0.09$) and base deficit 5.2 (1.8–15.7) mmol litre^{-1} compared with 3.5 (1.7–17.3) mmol litre^{-1} ($P < 0.05$), respectively). Thus continuous spinal anaesthesia was associated with greater haemodynamic stability and a slight improvement in fetal blood-gas tensions.

The median dose of intrathecal bupivacaine administered was 2.0 ml. Kestin and colleagues [5] gave a mean dose of 2.7 ml (range 1.5–7.4 ml) to achieve a similar level of block (T4). We felt that their initial dose (1.5 ml) was too large, as three of 20 women had a sensory block to T3 after this dose. Five women in the present study required more than 2.5 ml of bupivacaine and in each an adequate block was not achieved within 30 min. Kestin's group [5] also reported some patients who needed several increments of bupivacaine: one subject required a total of 7.4 ml. As an alternative to continued administration of the same local anaesthetic, various manoeuvres have been advocated, such as changing patient position, manipulating catheter position and switching to a different local anaesthetic [15, 16]. While the first two of these seem reasonable, there is no evidence to suggest that administration of a second drug is safer than additional doses of the first.

Much attention regarding the use of continuous spinal anaesthesia has been directed at the difficulties encountered inserting the 32-gauge catheter and the risk of postdural puncture headache. Most technical "failures" have been related to catheter kinking [17, 18]. We encountered this problem in three subjects (13%)—a rate consistent with the preliminary experience of other workers [17, 19]. With further experience, the failure rate appears to decrease to < 5 % [5]. Although the present series was small, no subject developed a headache typical of dural puncture. The incidence of postdural puncture headache with spinal catheters has varied from 1 % to 10 % [4, 5]. However, there have been no sizable studies of the use of 32-gauge catheters in obstetric patients to enable the true incidence of postdural puncture headache to be determined.

In conclusion, the results of the present study suggest that continuous spinal anaesthesia combines the reliability of subarachnoid injection and the advantages of repeatability, without the risk of reduction in maternal cardiac output and fetal pH. While these attributes may be valuable in some clinical situations, the advantages must be balanced against the increased cost of technique and the possible risk of neurotoxicity if excessive doses of local anaesthetic are required.

REFERENCES

1. Carrie LES. Extradural, spinal or combined block for obstetric surgical anaesthesia. *British Journal of Anaesthesia* 1990; **65**: 225–233.
2. Kestin IG. Spinal anaesthesia in obstetrics. *British Journal of Anaesthesia* 1991; **66**: 596–607.
3. Robson SC, Boys RJ, Rodeck C, Morgan B. Maternal and fetal haemodynamic effects of spinal and extradural anaesthesia for elective Caesarean section. *British Journal of Anaesthesia* 1992; **69**: 54–59.
4. Caritis SN, Abouleish E, Edelstone DI, Mueller-Heubach E. Fetal acid–base state following spinal and epidural anesthesia for Cesarean section. *Obstetrics and Gynecology* 1980; **56**: 610–615.
5. Kestin IG, Madden AP, Mulvein JT, Goodman NW. Comparison of incremental spinal anaesthesia using a 32-gauge catheter with extradural anaesthesia for elective Caesarean section. *British Journal of Anaesthesia* 1991; **66**: 232–236.
6. Easterling TR, Carlson LK, Schmucker BC, Brateng DA, Benedetti TR. Measurement of cardiac output in pregnancy by Doppler technique. *American Journal of Perinatology* 1990; **3**: 220–222.
7. Robson SC, Dunlop W, Moore M, Hunter S. Combined Doppler and echocardiographic measurement of cardiac output: theory and application in pregnancy. *British Journal of Obstetrics and Gynaecology* 1987; **94**: 1014–1027.
8. Trudinger BJ, Cook CM, Jones L, Giles WB. A comparison of fetal heart rate monitoring and umbilical artery waveforms in the recognition of fetal compromise. *British Journal of Obstetrics and Gynaecology* 1986; **93**: 171–175.
9. FDA Safety Alert: cauda equina syndrome associated with use of small-bore catheters in continuous spinal anesthesia. *Food and Drug Administration*; May 29, 1992.
10. Department of Health. United States Food and Drug Administration (US FDA): Withdrawal of approval for smallbore catheters used in continuous spinal anaesthesia. *Safety Action Bulletin; SAB(92) 49*; September 1992.
11. Rigler ML, Drasner K, Krejcie TC, Yelich SJ, Scholnick FT, DeFontes J, Bohner D. Cauda equina syndrome after continuous spinal anesthesia. *Anesthesia and Analgesia* 1991; **72**: 275–281.
12. Ross BK, Coda B, Heath CH. Local anesthetic distribution in a spinal model: a possible mechanism of neurologic injury after continuous spinal anesthesia. *Regional Anesthesia* 1992; **17**: 69–77.
13. Wildsmith W. Catheter spinal anesthesia and cauda equina syndrome: an alternative view. *Anesthesia and Analgesia* 1991; **73**: 368–369.
14. Lemmon WT, Paschal GW. Continuous-serial, fractional, controllable intermittent-spinal anesthesia, with observations on 1000 cases. *Surgery, Gynecology and Obstetrics* 1942; **74**: 424–429.
15. Bevacqua BK, Cleary WF, Slucky AV. Catheter spinal anesthesia and cauda equina syndrome: an alternative view. *Anesthesia and Analgesia* 1991; **73**: 367–368.
16. Drasner K, Rigler ML. Catheter spinal anesthesia and cauda equina syndrome: an alternative view. *Anesthesia and Analgesia* 1991; **73**: 366–370.
17. Hurley RJ, Lambert DH. Continuous spinal anesthesia with a microspinal technique: preliminary experience. *Anesthesia and Analgesia* 1990; **70**: 97–102.
18. Nagle CJ, McQuay HJ, Glynn CJ. 30-gauge spinal catheters through 26-gauge needles. *Anaesthesia* 1990; **45**: 1052–1054.
19. Kestin IG. Incremental spinal anaesthesia using a 32-gauge catheter. *British Journal of Anaesthesia* 1990; **65**: 280–281P.

British Journal of Anaesthesia 1993; 70: 639–641

SPREAD OF SPINAL ANAESTHESIA FOR CAESAREAN SECTION IN SINGLETON AND TWIN PREGNANCIES

B. JAWAN, J. H. LEE, Z. K. CHONG AND C. S. CHANG

SUMMARY

We have compared the spread of spinal anaesthesia in parturients with singleton and those with twin pregnancies. Fifty-five unpremedicated patients with uncomplicated pregnancy scheduled for Caesarean section were allocated to two groups: group I = 35 singleton mothers; group II = 20 with twin pregnancy. Both groups received spinal anaesthesia with hyperbaric bupivacaine 10 mg (2 ml of 0.5%). Mean birthweight was 3290 (SD 452) g and 5008 (495) g in groups I and II (combined birthweights), respectively. We found a statistically significant difference in onset and maximal cephalad spread of spinal anaesthesia (group I median T5, range T8–T4; group II T3, range T6–T2). The mechanisms of higher cephalad spread of spinal anaesthesia in parturients may be a decrease in cerebrospinal fluid volume secondary to shunting of blood from the obstructed inferior vena cava to the extradural venous plexus and increased nerve sensitivity to local anaesthetics because of increased concentrations of progesterone. The twin pregnancy group had heavier, larger uteri and greater daily production of progesterone. (Br. J. Anaesth. 1993; **70**: 639–641)

KEY WORDS

Anaesthetic techniques: spinal. Pregnancy: singleton, twins, Caesarean section.

Pregnancy is known to cause higher cephalad spread of spinal analgesia [1, 2]. However, it is not known if there is a difference in the degree of spread between those with twin pregnancy and those with a singleton fetus. This study compared the level of spread of spinal analgesia between these groups of women undergoing elective Caesarean section.

PATIENTS AND METHODS

After obtaining Hospital Ethics Committee approval and written informed consent from the patients, and excluding those parturients with history of hypertension and pre-eclampsia, we studied 55 unpremedicated women, ASA I–II, undergoing elective Caesarean section. Patients were allocated to two groups: group I consisted of 35 parturients with singleton pregnancy; group II, 20 women with twin pregnancy. All patients received spinal anaesthesia, through a 25-gauge disposable needle, comprising 0.5% hyperbaric bupivacaine 10 mg (Marcaine Heavy, Astra) via the L3–4 interspace in left decubitus position. Patients were given lactated Ringer's solution 1000 ml and placed in a supine position with 15° left tilt immediately after the spinal injection. The level of analgesia was checked using pinprick at 2, 4, 10, 14 and 20 min. By 20 min, most of the newborns were delivered. Systemic arterial pressure was measured using an automatic monitor (Dinamap, Criticon) every 5 min. If the systolic AP decreased by more than 20% of the initial value, or to less than 100 mm Hg, ephedrine 12 mg was given i.v. Other variables measured included abdominal circumference and fundus-to-symphisis distance, recorded on admission, and birthweight and placental weight, measured at delivery.

The volume of amniotic fluid was disregarded because accurate measurement was difficult. All data are expressed as mean (range or SD), except for the level of spinal analgesia which is expressed as median (range). Data were analysed using the Mann–Whitney *U* test for the level of spinal spread, unpaired *t* test for parametric data, and chi-square test for the incidence of hypotension. $P < 0.05$ was considered statistically significant.

RESULTS

Parturients with twins were significantly heavier (table I) and had significantly heavier (combined) infant birthweight (5008 (495) g *vs* 3290 (452) g) and placental weight (999 (128) g *vs* 678 (97) g) than those in the singleton group. Abdominal circum-

TABLE I. *Patient data (mean (range or* SD*))* *P < 0.05 *compared with group I*

	Age (yr)	Weight (kg)	Height (cm)
Group I ($n = 35$)	29 (19–36)	65.3 (7.4)	157 (4.3)
Group II ($n = 20$)	27.8 (23–41)	72.5 (12)*	159 (5.8)

B. JAWAN, M.D.; J. H. LEE, M.D.; Z. K. CHONG, M.D.; C. S. CHANG, M.D.; Department of Anesthesiology, Chang Gung Memorial Hospital, 123 Ta-Pei Road, Niao Sung Hsiang, Kaohsiung Hsien, Taiwan, R.O.C. Accepted for Publication: January 26, 1993.

TABLE II. *Birthweight of infants (BW), placenta weight (PW), fundus-to-symphisis distance (FSD) and abdominal circumference (AC) in the two groups (mean (SD)).* $*P < 0.05$ *compared with group I*

	BW (g)	PW (g)	FSD (cm)	AC (cm)
Group I	3290 (452)	678 (97)	35.8 (2)	97.2 (5.7)
Group II	5008 (495)*	999 (128)*	40.5 (6.7)*	102 (9.1)*

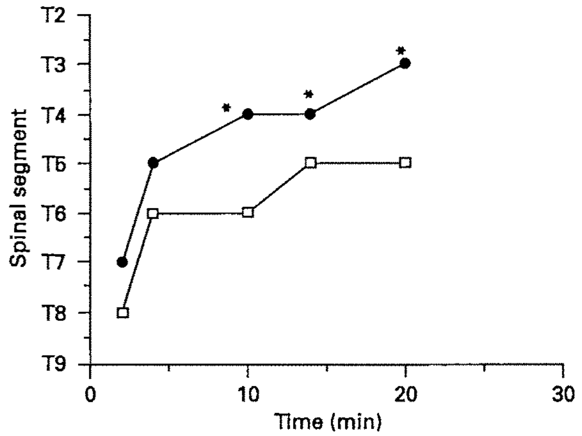


FIG. 1. Median cephalad spread of spinal analgesia in the singleton (□) and twin pregnancy (●) groups. $*P < 0.05$.

ference and fundus-to-symphisis distance were also larger in the twin group (table II). The number of patients who needed ephedrine did not differ between groups (57 % *vs* 65 %).

After 10 min, the onset and cephalad spread of spinal analgesia in twin parturients were significantly different than those for singletons ($P < 0.05$) (fig. 1). Spread was to T4 (T10–T3), T4 (T8–T2) and T3 (T6–T2) in the twin group and to T6 (T8–T4), T5 (T8–T4) and T5 (T8–T4) in the singleton group at 10, 14 and 20 min, respectively.

DISCUSSION

We observed that parturients with twin pregnancy had a heavier and larger gravid uterus and more rapid onset and higher cephalad spread of spinal analgesia during Caesarean section compared with those with a singleton pregnancy. Compression of the inferior vena cava (IVC) secondary to increased intra-abdominal pressure has been shown to be an important factor in higher cephalad spread of spinal analgesia [1, 2]—the resulting engorgement of the lumbar and vertebral veins causes a decreased subarachnoid space and smaller CSF volume, and with less spinal fluid present in the subarachnoid space, the same amount of drug causes higher spread inside the narrower space [1, 2]. The fact that CSF volume is an important factor in modifying the spread of spinal analgesia was evident also in our previous study in which, by artificially reducing the CSF volume before administration of spinal anaesthesia, we produced a significant increase in cephalad spread of the spinal block [3].

The incidence of maternal hypotension which required treatment was 20/35 (57 %) in the singleton group and 13/20 (65 %) in the twin group. The supine hypotension syndrome is not related to dose of anaesthetic or the level of spinal anaesthesia [4]. It may be caused by many factors such as occlusion of the IVC, direct compression of the aorta [5, 6], the number of venous collaterals [7], the level of compression [8], low pressure baroreceptors in the vena cava [9], and local sympathetic venoarteriolar reflex [10]. The failure to demonstrate a significant difference between the two groups in the incidence of hypotension does not imply that both groups had the same degree of IVC compression.

The sensitivity of nerve fibres to local anaesthetic agents during pregnancy has been studied extensively [11–13]. In the isolated intact vagus nerve of the pregnant rabbit, sensitivity was increased [12]. Pregnancy also increases peripheral median nerve sensitivity to lignocaine in humans [13]. Increased concentrations of progesterone during pregnancy are thought to be the cause of this increased nerve fibre sensitivity [13, 14]. The CSF concentration of progesterone is increased in parturients and a correlation has been found between the CSF concentration of progesterone and the dose requirement for intrathecal lignocaine [14]. Progesterone in human pregnancy is biosynthesized by syncytiotrophoblasts in the placenta [15]; parturients with twin pregnancy have a heavier placenta and seem to produce more progesterone than those with a singleton pregnancy. Thus nerve fibres in twin gestation may be more susceptible to local anaesthetics.

REFERENCES

1. Greene NM. *Physiology of Spinal Anesthesia*, 3rd Edn. Baltimore, London: Willians & Wilkins, 1981.
2. Barclay DL, Renegar OJ, Nelson EW. The influence of inferior vena cava compression on the level of spinal anesthesia. *American Journal of Obstetrics and Gynecology* 1968; **101**: 792–800.
3. Jawan B, Lee JH. The effect of removal of CSF on cephalad spread of spinal analgesia with bupivacaine. *Acta Anaesthesiologica Scandinavica* 1990; **34**: 452–454.
4. Ueland K, Gills RE, Hansen JM. Maternal cardiovascular dynamics. *American Journal of Obstetrics and Gynecology* 1968; **100**: 42–54.
5. Marx GF, Husain FJ, Shiau HF. Brachial and femoral blood pressures during the prenatal period. *American Journal of Obstetrics and Gynecology* 1980; **136**: 11–13.
6. Bieniarz J, Crottiogini JJ, Curuchet E, Romero-Salinar G, Yoshida T, Poseiro JJ, Caldeyno-Barcia R. Aortocaval compression by uterus in late human pregnancy. *American Journal of Obstetrics and Gynecology* 1968; **100**: 203–217.
7. Kerr MG, Scott DB, Samuel E. Studies of the inferior vena cava in late pregnancy. *British Medical Journal* 1964; **1**: 532–533.
8. Lotgering FK, Wallenburg HCS. Hemodynamic effect of caval and uterine venous occlusion in pregnant sheep. *American Journal of Obstetrics and Gynecology* 1986; **155**: 1164–1170.
9. Kostreva DR, Castaner A, Kampine JP. Reflex effects of hepatic baroreceptors on renal and cardiac sympathetic nerve activity. *American Journal of Physiology* 1980; **238**: R390.
10. Henriksen O, Amtrop O, Faris I, Agerskov K. Evidence for a local sympathetic veno arteriolar reflex in the dog hindleg. *Circulation Research* 1983; **52**: 534.
11. Fagraeus L, Urban BJ, Bromage PR. Spread of epidural analgesia in early pregnancy. *Anesthesiology* 1983; **58**: 184–187.

12. Datta S, Lambert DH, Gregus J, Gissen AJ, Covino BG. Differential sensitivity of mammalian nerve fibers during pregnancy. *Anesthesia and Analgesia* 1983; **62**: 1070–1072.
13. Butterworth JF, Waler FO, Lysa SZ. Pregnancy increases median nerve susceptibility to lidocaine. *Anesthesiology* 1990; **72**: 962–965.
14. Datta S, Hurley RT, Naulty JS, Stern P, Lambert DH, Conception M, Tulchinsky D, Weiss JB, Ostheimer GW. Plasma and cerebrospinal fluids progesterone concentrations in pregnant and non-pregnant women. *Anesthesia and Analgesia* 1968; **65**: 950–954.
15. Cunningham FG, MacDonald PC, Gant NF. The placental hormones. In: *Williams Obstetrics*, 18th Edn. New York: Prentice-Hall International Inc., 1989; 67–85.

British Journal of Anaesthesia 1993; 70: 642–646

DIRECT SPINAL EFFECT OF INTRATHECAL AND EXTRADURAL MIDAZOLAM ON VISCERAL NOXIOUS STIMULATION IN RABBITS

M. E. CRAWFORD, F. MOLKE JENSEN, D. B. TOFTDAHL AND J. B. MADSEN

SUMMARY

We measured alterations in a noxious visceromotor reflex in rabbits subjected to intestinal distension, after i.m., extradural or intrathecal injection of midazolam or saline. Spinal catheters were inserted and tunnelled surgically and the animals allowed to recover for 2 weeks. A balloon catheter was placed in the distal part of the descending colon, in the awake rabbit. Intraluminal pressures were increased continuously by water instillation until a sudden withdrawal of the pelvis was observed. Pressure values at withdrawal threshold were recorded immediately before the injection and after 5, 15 and 30 min. Pain thresholds were unaltered after saline. Extradural midazolam 12.5–250 $\mu g\ kg^{-1}$ *produced a dose-dependent increase in the percent maximum possible effect ranging from 7% after the smallest dose to 80%. Similar dose-dependent effects were observed after intrathecal injection of midazolam 25–62.5* $\mu g\ kg^{-1}$. *Extradural and intrathecal, but not i.v. injection of flumazenil 25* $\mu g\ kg^{-1}$ *(a benzodiazepine receptor antagonist) reduced the antinociceptive effect of extradural and intrathecal midazolam to pretreatment levels. A segmental effect of intrathecal midazolam was demonstrated using transcutaneous electrical stimulation in the areas of the neck and the lower back. The effect of intrathecal midazolam 62.5* $\mu g\ kg^{-1}$ *was restricted to the lumbar region, demonstrating a selective action on the spinal cord. Thus extradural and intrathecal midazolam produced a dose-dependent effect on the reflex response to visceral distension in rabbits. This effect is caused by a direct spinal action on benzodiazepine receptors in the spinal cord. (*Br. J. Anaesth. 1993; **70**: 642–646)

KEY WORDS

Anaesthetic techniques: intrathecal, extradural. Pain: visceral, intestinal distension. Pharmacology: midazolam, flumazenil.

Benzodiazepine binding sites are located in the spinal cord [1], with the greatest density of binding sites found within lamina II of the dorsal horn [2]. This region plays an important role in the processing of noxious information. Based on radioligand binding assays and electrophysiological studies, the benzodiazepine binding site appears linked to the $GABA_A$ receptor complex [3].

Benzodiazepines are known to enhance GABA-induced responses of central nervous system neurones *in vitro* [4–6]. Bicuculline, a $GABA_A$ receptor antagonist, has been shown to attenuate the antinociceptive effect of intrathecal midazolam, a water soluble benzodiazepine [7,8]. GABA may play an important role in the modulation of noxious stimuli, as administration of the $GABA_A$ agonist tetrahydro-isoxazolo-pyridinol (THIP) produces antinociception [9]. In addition, midazolam possesses analgesic properties when administered extradurally in humans [10] and intrathecally in rats [8,11–13]. The antinociceptive properties of midazolam appear to be dependent on the type of noxious stimulus used, as it is inactive in the tail flick test [12] and elicits only a weak effect when assessed in the hot-plate tests, in a dose range which lacks additional motor impairment [14].

We evaluated the effect of midazolam, a water soluble benzodiazepine, against visceral noxious stimuli in rabbits and determined if it produced a direct effect on the spinal cord, evaluated by the visceromotor response elicited by intestinal distension.

MATERIALS AND METHODS

The study was approved by the Danish Committee for Animal Research under the Department of Justice and was carried out in accordance with the ethical guidelines for investigation of experimental pain in conscious animals.

Eighteen female New Zealand albino rabbits, body weight 3.5–4.0 kg, were studied.

Catheter implantation

The animals were anaesthetized with a combination of i.m. ketamine 25 mg and xylazine 10 mg, supplemented with 1% lignocaine 5 ml administered s.c. into the area of the skin incision. The skin between L5 and L7 had been shaved previously and disinfected with alcohol. After skin incision the muscular fascia was opened, muscles bluntly detached from the spinous processes and haemostasis obtained by compression. After visualization of the

---

M.E. CRAWFORD, M.D.; F. MOLKE JENSEN, M.D.; Department of Anaesthesioloy, Hvidovre Hospital, University of Copenhagen, Kettegaards Alle, 2650 Hvidovre, Denmark. D.B. TOFTDAHL, M.D.; J.B. MADSEN, M.D.; The Danish Laboratory of Pain Research, Spanagervej 12, 4623 LI. Skensved, Denmark.
Accepted for Publication: January 21, 1993.

Correspondence to F.M.J.

ligamentum flavum between the spinous process of L7 and the caudal articular process of L6, a superficial incision was performed in the ligament, and a Portex extradural catheter, o.d. 0.9 mm, inserted and advanced 5 cm cranially. Correct extradural placement produced a rubber-like resistance during insertion. The catheter was secured with a drop of histacrylic glue. The muscular fascia was closed around the catheter and the free end mounted with a detachable Luer lock connector to which a rubber injection membrane had been attached. This end was positioned s.c. and dorsally between the forelegs. The skin was sutured and the animal left for 1–2 weeks; each was in a spacious wooden cage and with free access to food and water.

Intrathecal catheters were inserted using the same procedure except for the incision in the ligamentum flavum. Using a 21-gauge needle, an incision was made through the ligament and dura, resulting in a free flow of cerebrospinal fluid.

Animals presenting any signs of motor dysfunction after catheter implantation were excluded from the study. Cathether position was tested with 1% lignocaine. Injection of 1% lignocaine 0.5 ml extradurally produced weakness of the hindlimbs, whereas 1.5 ml resulted in total paralysis of the same limbs of the extradural batch. Total paralysis was obtained with 0.5 ml of the same solution in all animals of the intrathecal group. Six rabbits had extradural catheters implanted, six had intrathecal catheters and six rabbits were allocated to the group for i.m. injection. One animal in the last group suffered intestinal rupture because of a sudden increase in balloon pressure in the early phase of the study and was excluded and killed immediately.

Tests

The experimental method has been described earlier [15]. In brief, it consisted of a closed circuit containing water. A latex rubber balloon-tipped PVC catheter was used (William Cook, Europe), with an outer diameter of 0.2 cm and a double lumen providing the possibility of simultaneous water infusion and continuous pressure recording inside the balloon. All pressures were measured by a transducer with concomitant paper recording of the pressure curve. A stop-cock and a 20-ml syringe attached allowed a rapid reduction of pressure to 0 after pelvic withdrawal. The balloon catheter was introduced approximately 8 cm into the colon from the anus. Cut-off pressure was set at 100 mm Hg to avoid intestinal rupture.

With a water infusion rate of 15 ml min^{-1}, balloon pressure was increased until a sudden pelvic withdrawal by the rabbit was seen. The maximum intraluminal pressure at the time of this reaction was used to calculate test and control values. This procedure was repeated four times, 30 s apart.

Two investigators performed these measurements: one made the injection, restrained the rabbits loosely during introduction of the balloon, made a note on the recorder of the pressure at which pelvic withdrawal occurred, and emptied the balloon; the other investigator introduced the balloon catheter and observed the rabbit during distension of the balloon. At the time of the visceromotor reflex, this information was passed to the first investigator, who marked it on the recorder. In this way, the experiments were performed blinded to the observer of the visceromotor reflex. Furthermore, this observer was unaware of the drug, dose and route of administration used.

The test and control values were calculated as the mean of the last three measurements, because they had been found in a previous study to be more consistent [15]. In the dose–response study, thresholds were converted for each rabbit to percentage maximum possible effect (%MPE):

$$\%\text{MPE} = \frac{\text{test value} - \text{control value}}{100 - \text{control value}} \times 100$$

where control value = threshold obtained before injection; test value = threshold obtained after drug administration. The cut-off pressure was 100 mm Hg.

Pressure values were recorded before and at 5, 15 and 30 min after intrathecal injections, and at 15 and 30 min for extradural and i.m. injections. The 5-min measurement was avoided in the extradural and i.m. groups in order to allow diffusion of the drugs to the central nervous system. Transcutaneous electrical stimulation was performed via two metal skin electrodes, 2 cm apart. The rabbits were tested in the neck and lower back regions. Electrical energy was applied with a TENS stimulator which provided a constant current over a wide range of skin resistance (Elpha 500, Biometer, DK). Threshold values were defined as the current necessary to produce escape behaviour, expressed in mA, and calculated as the mean of three consecutive measurements.

Drug regimen

The dose–response relationship was assessed utilizing extradural doses of midazolam 250, 125, 25 and 12.5 µg/kg body weight and intrathecal doses of midazolam 62.5 and 25 µg kg^{-1}. I.m. doses were 250 and 62.5 µg kg^{-1}. The extradural doses of midazolam were chosen from pilot experiments preceding this study. The initial intrathecal dose was 25 µg kg^{-1} and increased to 62.5 µg kg^{-1} in order to obtain near maximal effect. The i.m. doses were chosen to correspond to the largest doses of intrathecal and extradural injections.

Drug injections were performed in volumes of 1.5 ml for extradural, 0.5 for intrathecal and 1.0 ml for i.m. injections. Previous studies in our laboratory have shown these volumes to give a distribution of injectate to T4 [16]. All placebo injections consisted of isotonic saline. The benzodiazepine antagonist, flumazenil (Ro 15-1788), was injected into animals in the extradural and intrathecal groups after administration of midazolam in order to evaluate if the effects observed were receptor mediated. Flumazenil injections were either parenteral or spinal (extradural or intrathecal). The dose was 25 µg/kg body weight for both routes of administration. This dose was the largest obtainable with the commercial solution of flumazenil given in a volume of 1 ml and was chosen in order to ensure antagonism of the effects after intrathecal and extradural midazolam.

Statistical methods

Data were analysed using the Wilcoxon rank sum

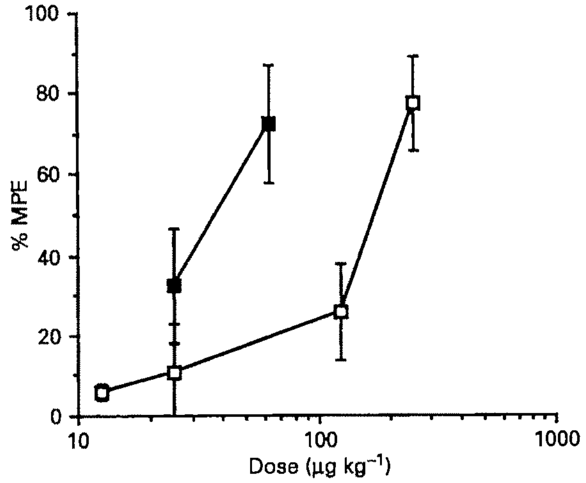


FIG. 1. Dose response 15 min after extradural (□) and intrathecal (■) midazolam: visceromotor reflex (percent of maximal possible effect (% MPE)) elicited by intestinal distension in rabbits. Each point represents mean, SEM; $n = 6$ in both groups.

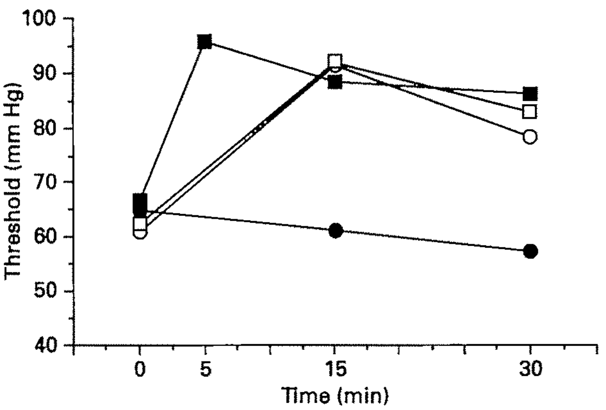


FIG. 2. Increase in intestinal distension thresholds after intrathecal (■) ($n = 6$), extradural (□) ($n = 6$) and i.m. (● = 62.5 μg kg^{-1}; ○ = 250 μg kg^{-1}) ($n = 5$) midazolam. Each point represents mean values. SEM values are omitted for clarity.

test for paired data and Mann–Whitney U test for unpaired data. When more than two groups were compared, the Friedmann two-way ANOVA was used, allowing for multiple testing within the group, when $P < 0.05$. This level of significance was chosen throughout the study.

RESULTS

None of the animals had signs of localized or generalized infection, or signs of motor dysfunction produced by catheter implantation. Body weights were comparable in the three groups.

Extradural or intrathecal injection of lignocaine showed that all catheters were placed correctly.

Saline injections

Injection of isotonic saline 1.5 ml in the extradural and 0.5 ml in the intrathecal group did not produce significant change in threshold to intestinal distension (4.9 (SEM 8.2) % and 0.2 (5.2) % change after extradural and intrathecal saline, respectively).

Extradural administration of midazolam

Extradural midazolam produced a dose-dependent response in the visceral response threshold (fig. 1). The effect of the applied doses was $250 \gg 125 > 25 = 12.5 =$ saline ($P < 0.05$, Wilcoxon rank-sum test, Friedmann test). After the maximal dose of midazolam, there were signs of slight motor impairment in one rabbit, judged by the ability of the animal to walk.

The ability to jump evoked by provocation remained intact. This effect on the motor system lasted for approximately 10 min, thus at the first test 15 min after injection no signs of motor impairment were present. Muscular rigidity was not observed.

Intrathecal administration

The dose–response relationship after midazolam 25 and 62.5 μg kg^{-1} is shown in figure 1. The effect after the large dose was significantly different from placebo at all times (fig. 2), whereas the effect after 25 μg kg^{-1} reached significance only at 5 min after administration (not illustrated). The increase produced by midazolam 62.5 μg kg^{-1} was prolonged and remained stable during the study (fig. 2).

The extradural dose was approximately five times larger than the intrathecal dose required for a 50 % increase in MPE (calculated from figure 1).

I.m. administration

Midazolam 250 μg kg^{-1} produced mean increases in distension thresholds comparable to those observed after extradural administration of the same dose (fig. 2). The smaller dose, 62.5 μg kg^{-1}, produced an insignificant decrease in the distension threshold at 15 and 30 min.

Segmental effect

Using the electrical stimulation test, intrathecal midazolam 62.5 μg kg^{-1} elicited a significant increase in escape threshold in the lumbar region (before: 17.0 (1.3) mA; after 15 min: 21.6 (1.6) mA; 30 min: 21.2 (2.3) mA) ($P < 0.05$), whereas in the cervical region thresholds remained unaltered (9.5, 9.1 and 9.7 mA, before, after 15 and 30 min, respectively) (fig. 3).

Duration of response

The effect was significantly increased throughout the 30-min study period after intrathecal, extradural and the large i.m. dose of midazolam (fig. 2).

Antagonist

After i.v. administration of flumazenil 25 μg kg^{-1}, distension thresholds after extradural and intrathecal midazolam remained virtually unaltered (fig. 4). The same dose of antagonist extradurally and intrathecally not only abolished the response after midazolam administered by the same route (fig. 4), but reduced the distension threshold to less than control values (fig. 4).

Behavioural results

Before each retraction of the pelvis, the rabbit usually showed signs of awareness to the distending stimulus—sitting still, movement of the tail and redness of the ears. These reactions were also observed after administration of midazolam; no other signs of sedation were observed. There were no signs of scratching or biting the lower extremities.

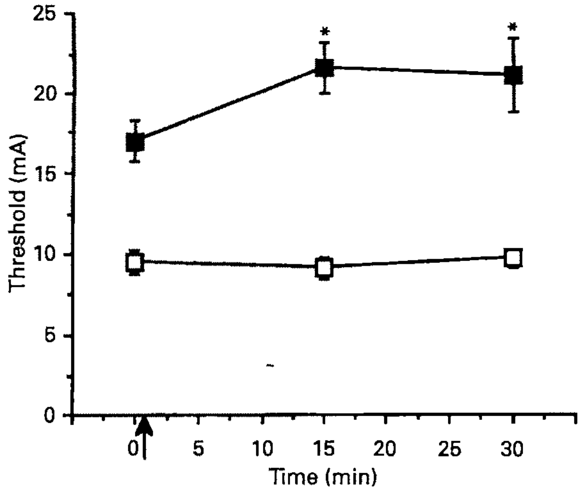


FIG. 3. Changes in electrical stimulation thresholds (mean, SEM) after intrathecal midazolam 62.5 $\mu g\ kg^{-1}$. ■ = Lumbar region; □ = cervical region. Arrow indicates injection time. $^*P < 0.05$ compared with control values.

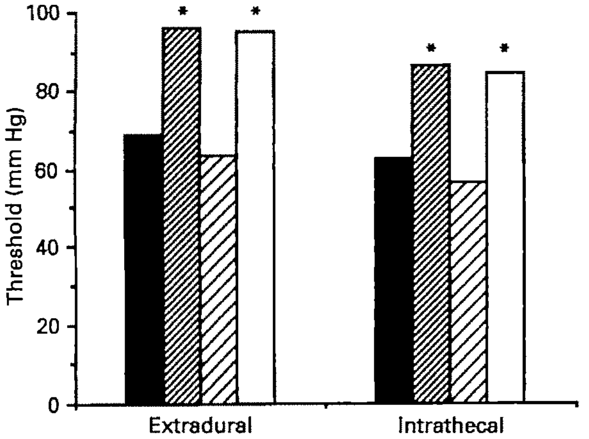


FIG. 4. Effect of extradural or intrathecal (▨) and i.v. (□) flumazenil 25 $\mu g\ kg^{-1}$ on extradural midazolam 250 $\mu g\ kg^{-1}$ (left) and intrathecal midazolam 62.5 $\mu g\ kg^{-1}$ (right) antinociception against intestinal distension. (In columns ▨, spinal flumazenil was administered by the same route as the midazolam.) ▨ = Midazolam alone. ■ = Values before drug administration (control). $^*P < 0.05$ compared with control.

DISCUSSION

Distension of the colon of the rabbit has been shown to be a reliable and reproducible method of eliciting visceral noxious stimuli in rabbits [15]. This method has been used in several other species, including man, and similar reproducible results were obtained (for review see [17]). The end-point of the test, pelvic withdrawal, depends on normal function of the motor system. In the present study, signs of motor impairment were observed in one rabbit for 10 min (slight dysco-ordination of the hindlimbs during walking, but with an intact ability to jump). At the 15-min time of testing there were no signs of motor impairment. Thus the possible effects on motor function did not occur to any extent after the doses of midazolam used. In a pilot study performed to determine the dose range for the present study, extradural midazolam 1000 $\mu g\ kg^{-1}$ produced a flaccid paralysis of the hindlimbs for approximately 1 h in all rabbits. This dose is four times the maximum dose used in this study and these results are in accordance with the results obtained by Yanez and co-workers [14], who also observed paralysis in rats given approximately six times the antinociceptive dose of midazolam.

A receptor link between the $GABA_A$ site and the benzodiazepine site in the spinal cord has been described earlier [3]. Recent work by Edwards and co-workers [8] confirmed this linkage. They found that bicuculline, a $GABA_A$ receptor antagonist, was able to attenuate the effect of spinally administered midazolam.

This fact, combined with the antinociceptive effect after intrathecal administration of THIP, a specific $GABA_A$ agonist [9], supports a physiological and an anatomical link between the two receptors. This link may also be responsible for the motor effects observed after larger doses of intrathecal and extradural midazolam. The existence of GABA receptors on motor neurone membranes in combination with a link with the benzodiazepine receptor explains the antispastic effect of benzodiazepines.

In the present study, extradurally and intrathecally administered midazolam produced a dose-dependent, pronounced effect against visceral noxious stimulation. The apparently increased potency after intrathecal compared with extradural midazolam is in accordance with experience from human studies, in which morphine 0.5 mg intrathecally appeared equianalgesic with extradural morphine 2–4 mg.

The effects of midazolam were antagonized by the benzodiazepine antagonist flumazenil, but only after concomitant extradural or intrathecal administration and not by i.v. administration. These observations, in combination with the greater efficacy following intrathecal administration of midazolam and the segmental analgesia obtained in the electrical stimulation test, strongly suggest a selective spinal action of extradural and intrathecal midazolam. Furthermore, if the antagonist action of intrathecal and extradural flumazenil were caused by a central distribution to the brain, one would expect parenteral administration of flumazenil to exert at least some degree of antagonism against both intrathecal and extradural midazolam. The direct spinal action of midazolam has been confirmed in previous studies [8,12,13].

The antinociceptive effect after the largest i.m. midazolam dose, 0.25 $mg\ kg^{-1}$, could be mediated via a local action on the spinal cord, as midazolam penetrates the blood–brain barrier easily. The reduction in thresholds after parenteral injection of a small dose of midazolam (62.5 $\mu g\ kg^{-1}$) supports this hypothesis and is in accordance with the work by Daghero, Bradley and Kissin [18]. They found that small doses of midazolam in the spinal cord produced analgesia, whereas small doses in the brain produced hyperalgesia. The hypothesis by Fields, Heinricher and Mason [19] concerning on- and off-cells in the rostral ventromedial medulla (RVM) exerting a descending control of noxious stimuli at the level of the spinal cord and the inhibition of off-cells by GABA resulting in hyperalgesia, is in accordance with present and previous observations of various effects after benzodiazepines: they are able to attenuate opioid-induced antinociception [20] and produce hyperalgesia when administered parenterally or in the brain, but elicit antinociception when they are administered locally at the spinal cord.

The reduction in distension thresholds to less than control values obtained by intrathecal administration of flumazenil $25\ \mu g\ kg^{-1}$ could implicate a tonic active GABA–benzodiazepine system in the modulation af visceral pain. This hypothesis is supported by the work of Edwards and co-workers [8], who found that bicuculline, a $GABA_A$ antagonist, produced hyperalgesia together with allodynia, when given intrathecally in rats. Ness and Gebhart [21] have recently discovered the existence of a descending inhibitory system of neurones in the spinal cord, which are excited by colorectal distension. The inhibition originated from areas in both the periaqueductal grey matter and the RVM.

The effect after intrathecal midazolam appears to be dependent on both the nociceptive test used and the choice of species. Yanez and co-workers [14] found morphine to be approximately 15 times as effective as midazolam on a molar basis, when using the hot-plate test in rats. Serrao and co-workers [13] found fentanyl was only five times as effective as midazolam against electrical stimulation in rats, whereas they found no effect of midazolam on the tail-flick response. The present results compared with unpublished data from our laboratory reveal midazolam to be approximately 20 times as effective as morphine against intestinal distension in rabbits. These differences in effect after morphine and midazolam on different noxious stimuli are physiological evidence of the anatomical separation of intraspinal pathways of visceral and somatic afferent fibres [22,23]. The results obtained in this study have not confirmed those of a preliminary study in humans [24], in which different doses of intrathecal midazolam were found to be effective against per- and postoperative somatic pain and ineffective against sympathetic reflexes produced by manipulation of abdominal contents and against postoperative pain of assumed visceral origin. The preliminary nature of this study, the differences in methods of visceral stimulation and the different species studied make comparison impossible, but point to the need for further studies in humans to determine the effects of spinally applied midazolam on different types of visceral pain.

ACKNOWLEDGEMENTS

This study was financed with a grant from Hoffmann–la Roche, Copenhagen. We thank Birgit O. Mikkelsen, M.SC., of Hoffmann–la Roche for theoretical support and for supplying the test drugs, Professor Tony L. Yaksh for constructive criticism and Peter Urban for assistance. William Cook, Europe, produced the balloon catheters.

REFERENCES

1. Möhler J, Okada T. Benzodiazepine receptor: Demonstration in the central nervous system. *Science* 1977; **198**: 849–851.
2. Faull RLM, Villiger JW. Benzodiazepine receptors in the human spinal cord; a detailed anatomical and pharmacological study. *Neuroscience* 1986; **17**: 791–802.
3. Unnerstal JR, Kuhar MR, Niehoff, DL, Palacios JM. Benzodiazepine receptors are coupled to a subpopulation of GABA receptors: Evidence from a quantative autoradigraphic study. *Journal of Pharmacology and Experimental Therapeutics* 1981; **218**: 797–804.
4. Choi DW, Farb DH, Fischbach GD. Chlordiazepoxide selectively augments GABA action in spinal cord cell cultures. *Nature (London)* 1977; **269**: 342–344.
5. MacDonald R, Barker JL. Benzodiazepines specifically modulate GABA mediated postsynaptic inhibition in cultured mammalian neurons. *Nature (London)* 1978; **271**: 563–564.
6. Nistri A, Constanti A. Effects of flurazepam on amino acid evoked responses recorded from the lobster muscle and the frog spinal cord. *Neuropharmacology* 1978; **17**: 127–135.
7. Cheng SC. Metabolic compartmentation of the GABA system, relationship of GABA metabolism to anesthesia. In: Mandel P, DeFeudis FV, eds. *GABA–Biochemistry and CNS Function*. New York: Plenum Press, 1979; 161–175.
8. Edwards M, Serrao JM, Gent JP, Goodchild CS. On the mechanism by which midazolam causes spinally mediated analgesia. *Anesthesiology* 1990; **73**: 273–277.
9. Christensen AV, Larsen JJ. Antinoceptive and anticonvulsant effect of THIP, a pure GABA agonist. *Polish Journal of Pharmacology and Pharmacy* 1982; **34**: 127–134.
10. Rigoli M. Epidural analgesia with benzodiazephines. In: Tiengo M, Cousins MJ, eds. *Clinical Pharmacology of New Analgesics and Anesthetics*. New York: Raven Press, 1983; 69.
11. Mantagazza P, Parenti M, Tammiso R, Vita P, Zambotti F, Zonta N. Modification of the antinociceptive effect of morphine by centrally administered diazepam and midazolam. *British Journal of Pharmacology* 1982; **75**: 569–572.
12. Goodchild CS, Serrao JM. Intrathecal midazolam in the rat. Evidence for a spinally mediated analgesia. *British Journal of Anaesthesia* 1987; **59**: 1563–1570.
13. Serrao JM, Stubbs SC, Goodchild CS, Gent JP. Intrathecal midazolam and fentanyl in the rat: evidence for different antinociceptive effect. *Anesthesiology* 1989; **70**: 780–786.
14. Yanez A, Sabbe MB, Stevens CW, Yaksh TL. Interaction of midazolam and morphine in the spinal cord of the rat. *Neuropharmacology* 1990; **29**: 359–364.
15. Jensen FM, Madsen JB, Ringsted CR, Christensen AA. Intestinal distention test, a method for evaluating intermittent visceral pain in the rabbit. *Life Sciences* 1988; **43**: 747–754.
16. Madsen JB, Jensen FM, Faber T, Bille-Hansen V. Chronic catherization of the epidural space in rabbits: a model for behavioural and histopathological studies. Examination of meptazinol neurotoxicity. *Acta Anaesthesiologia Scandinavica* 1993; (in press).
17. Ness TJ, Gebhart GF. Visceral pain: a review of experimental studies. *Pain* 1990; **41**: 167–234.
18. Daghero AM, Bradley EL, Kissin I. Midazolam antagonizes the analgesic effect of morphine in rats. *Anesthesia and Analgesia* 1987; **66**: 944–947.
19. Fields HL, Heinricher MM, Mason P. Neurotransmitters in nociceptive modulatory circuits. *Annual Review of Neuroscience* 1991; **14**: 219–245.
20. Rosland JH, Hole K. 1,4-Benzodiazepines antagonize opiate-induced antinociception in mice. *Anesthesia and Analgesia* 1990; **71**: 242–248.
21. Ness TJ, Gebhart GF. Quantitative comparison of inhibition of visceral and cutaneous spinal nociceptive transmission from the midbrain and medulla in the rat. *Journal of Neurophysiology* 1987; **58**: 850–865.
22. Cervero F. Visceral nociception: Peripheral and central aspects of visceral nociceptive systems. *Philosophical Transactions of the Royal Society of London (Biology)* 1985; **308**: 325–337.
23. Ness TJ, Gebhart GF. Differential effects of morphine and clonidine on visceral and cutaneous spinal nociceptive transmission in the rat. *Journal of Neuropharmacology* 1989; **62**: 220–230.
24. Goodchild CS, Noble DJ. The effects of intrathecal midazolam on sympathetic nervous system reflexes in man—a pilot study. *British Journal of Clinical Pharmacology* 1987; **23**: 279–285.

British Journal of Anaesthesia 1993; 70: 647–653

CARDIOVASCULAR EFFECTS OF I.V. INDUCTION IN CHILDREN: COMPARISON BETWEEN PROPOFOL AND THIOPENTONE

C. S. T. AUN, R. Y. T. SUNG, M. E. O'MEARA, T. G. SHORT AND T. E. OH

SUMMARY

We have compared the haemodynamic responses to i.v. propofol 2.5 mg kg^{-1} with those to thiopentone 5.0 mg kg^{-1} in 41 healthy Chinese children at induction of anaesthesia. They were allocated to four groups according to their age and induction agent received: group I < 2 yr, propofol, n = 9; group II < 2 yr, thiopentone, n = 9; group III 2–12 yr, propofol, n = 12; group IV 2–12 yr, thiopentone, n = 11. Anaesthesia was maintained by spontaneous ventilation with 70% nitrous oxide and 0.5% halothane in oxygen. Arterial pressure and heart rate were monitored by automatic oscillotonometer. Stroke volume was measured by two-dimensional echocardiography and pulse Doppler. Measurements were made before induction and at 1-min intervals for 5 min after induction. The reduction in mean arterial pressure was significantly greater after propofol (28–31%) than after thiopentone (14–21%) (P = 0.001). The reduction in cardiac index (10–15%) after induction was not significantly different between the two agents (P = 0.122). Baroreflex mediated increases in heart rate and systemic vascular resistance were less after propofol than after thiopentone. The baroreceptor reflex was more attenuated in children aged less than 2 yr than in older children. (Br. J. Anaesth. 1993; **70**: 647–653)

KEY WORDS

Anaesthetics: intravenous, propofol, thiopentone. Anaesthesia: paediatric. Heart: cardiac output. Measurement techniques: echocardiography.

Induction of anaesthesia with propofol is associated with a significantly greater reduction in arterial pressure than with thiopentone, both in adults [1–4] and in children [5–7]. This is one of the main criticisms of the use of propofol. In adults, the mechanism of hypotension has been studied by the invasive thermodilution method [2, 4, 8, 9]. The primary mechanism appears to be a reduction in systemic vascular resistance. There is controversy about its direct cardiovascular effects. However, it appears to exert a mild negative inotropic effect. Because of ethical and technical constraints, haemodynamic data in children are limited to non-invasive measurements of heart rate and arterial pressures [5–7], but these peripheral haemodynamic measurements are inadequate to describe the myocardial effects of anaesthetic agents [10]. With the development of echocardiography it is now possible to measure cardiac output non-invasively with accuracy by combining the technology of echocardiography and the Doppler principle. Measurement of cardiac output using the technique of pulsed Doppler echocardiography has been shown to have a high correlation coefficient ($r = 0.90–0.98$) compared with the dye dilution technique [11, 12]. In this study, this technique was used to compare the cardiovascular effects of i.v. induction of anaesthesia with either propofol or thiopentone in Chinese children.

PATIENTS AND METHODS

The study was approved by the Clinical Research Ethics Committee of the Chinese University of Hong Kong. We studied 45 healthy Chinese children aged between 8 months and 12 yr (ASA I or II) scheduled for elective surgery. Informed consent was obtained from their parents. Children with a history of allergy, or of any adverse reactions to previous anaesthetics were excluded. Those children in whom pre-induction haemodynamic variables or venous cannulation could not be obtained were withdrawn from the study. All patients were premedicated with oral diazepam syrup 0.4 mg kg^{-1} and EMLA cream (lignocaine 25 mg g^{-1} and prilocaine 25 mg g^{-1}, Astra pharmaceuticals, Sweden) applied to the dorsum of both hands approximately 2 h before anaesthesia. The children were grouped into two age groups: less than 2 yr and between 2 and 12 yr. Children in each age group were allocated randomly in a double-blind manner to receive either propofol 2.5 mg kg^{-1} or thiopentone 5 mg kg^{-1}.

On arrival in the anaesthetic room, a non-invasive automatic pressure monitor (Dinamap 845 XT,

---

C. S. T. AUN, M.B., B.S., F.R.C.ANAES., M. E. O'MEARA*, M.B., CH.B., F.R.C.ANAES., T. G. SHORT, M.B., CH.B., F.A.N.Z.C.A., T. E. OH, M.D., F.R.C.P. (ED.), F.R.C.ANAES., F.A.N.Z.C.A. (Department of Anaesthesia and Intensive Care); R. Y. T. SUNG, M.B., M.SC., M.R.C.P. (Department of Paediatrics); Prince of Wales Hospital, The Chinese University of Hong Kong, Shatin, New Territories, Hong Kong.

Accepted for Publication: December 15, 1992.

*Present address: Department of Anaesthesia, Addenbrookes Hospital, Hills Road, Cambridge.

Critikon Inc., Florida, U.S.A.) was applied to one arm, and a 24-gauge cannula was inserted into a vein in the opposite hand, where an oximeter probe (Satlite, Datex Instrumentarium Corp., Helsinki, Finland) was attached for continuous monitoring of arterial oxygen saturation. The child was allowed to settle and baseline haemodynamic measurements obtained. The child was noted to be either calm or agitated at this stage. After baseline recordings, the appropriate i.v. agent was injected over a period of 20 s. One percent lignocaine 0.05 ml was added to each 1 ml of propofol immediately before administration. As soon as the child was asleep, a face mask was applied and anaesthesia maintained with 70% nitrous oxide and 0.5% halothane in oxygen using a Jackson–Rees modified Ayre's T piece. Haemodynamic variables were monitored at 1-min intervals for 5 min from the end of i.v. injection. End-tidal carbon dioxide concentration was monitored using a mainstream capnometer (HP 78356A, Hewlett–Packard, California, U.S.A.) attached to the face mask. Fresh gas flow was adjusted and ventilation assisted if necessary to maintain end-tidal carbon dioxide concentration at 4.7–6.0 kPa.

Arterial pressure and heart rate were recorded by the Dinamap. Stroke volume was obtained by an ultrasound scanning device (Aloka-280, Aloka Co., Ltd., Tokyo, Japan) using a handheld Doppler probe of 5 MHz. An initial two-dimensional echocardiogram was scanned along the parasternal longitudinal axis to obtain the internal aortic diameter at the aortic annulus. Three measurements were performed and the average was taken as the aortic diameter. Pulsed-wave Doppler signals from the ascending aorta were identified and recorded by placing the transducer probe at the suprasternal notch. The transducer was positioned to align the transmitted sound beam as parallel as possible to the velocity vector of the blood flow. All the computations were performed by the built-in program of the ultrasound scanner. The Doppler recordings and ECG tracings were recorded on videotape and analysed at a later time.

The velocity of the blood flow was calculated by the Doppler equation:

$$V = \Delta fc/2fo$$

Any deviation of the transducer from the parallel axis of more than 20° angle was corrected by the formula:

$$V = \Delta fc/2fo \operatorname{Cos}\theta$$

where V = velocity of blood flow; Δf = change in frequency; c = sound velocity in the blood; fo = transmitting frequency; θ = angle of insonance or the angle between the beam of ultrasound and the direction of blood flow.

Stroke volume (SV) was computed by multiplying the average time velocity integral by aortic cross-sectional area using the formula:

$$\mathrm{SV} = \mathrm{CSA} \sum_{t=0}^{t=\mathrm{ET}} V\Delta t$$

where CSA = cross sectional area of aorta, V = velocity, t = sampling interval, ET = ejection time.

The stroke volume was calculated by averaging the measurements obtained from three consecutive cardiac cycles. All Doppler recordings and measurements were performed by a single observer (R.Y.T.S.), who was blind to the medication given.

Derived haemodynamic variables calculated from the measured variables included cardiac output, stroke volume index and cardiac index. Cardiac output was calculated as the product of stroke volume and heart rate. Surface area was derived from a nomogram for infants and children [13]. Systemic vascular resistance (SVR) was calculated using the following formula [14]:

$$\mathrm{SVR}\ (\mathrm{dyn\ s\ cm^{-5}}) = \frac{\text{mean arterial pressure}}{\text{cardiac output}} \times 80$$

In order to compare the effects of two agents in two age groups of children, the patients were allocated to four groups:

group I: toddlers younger than 2 yr who received propofol;

group II: toddlers younger than 2 yr who received thiopentone;

group III: children aged 2–12 yr who received propofol;

group IV: children aged 2–12 yr who received thiopentone.

Patient data between the same age groups were compared using a two-tailed Student's t test. The number of agitated children and the incidence of side effects were analysed by chi-square test. The baseline haemodynamic variables were compared by one-way analysis of variance. The haemodynamic measurements after induction were analysed using repeated measures analysis of variance for the difference from the baseline values. The factors included were time after induction, anaesthetic agents and age interaction. In the absence of statistically significant age-by-anaesthetic agent interactions, data from the four groups were compared simultaneously in the results. $P < 0.05$ was considered as statistically significant.

RESULTS

Four cases were excluded from the analysis because of inadequate Doppler recordings. Of the 41 patients studied, 18 were toddlers (nine in group I, nine in group II), and 23 were older children (12 in group III and 11 in group IV). Patient data and the ratio of agitated to calm children in each group are listed in table I. There were no statistically significant differences in mean age, body weight and surface area between groups I and II or between groups III and IV. In groups III and IV, there were more girls. There were more anxious children ($P = 0.01$) in groups I and II when compared with groups III and IV (table I).

Baseline haemodynamic variables were not significantly different between groups I and II or between groups III and IV (table II). The mean heart rates were greater ($P = 0.001$) and systemic vascular resistance values greater ($P = 0.003$) in the toddlers (groups I and II) than their respective values in the

TABLE I. *Patient characteristics (mean (range or* SD*)). Group I = less than 2 yr, propofol; group II = less than 2 yr, thiopentone; group III = 2–12 yr, propofol; group IV = 2–12 yr, thiopentone. BSA = Body surface area; Mood (a : c) = number of children agitated or calm.* *P < *0.05*

	Group I ($n = 9$)	Group II ($n = 9$)	Group III ($n = 12$)	Group IV ($n = 11$)
Age (yr)	1.2 (0.7–2)	1.1 (0.7–2)	5.2 (2–12)	4.4 (2–12)
Sex (M:F)	9:0	7:2	10:2	6:5
Weight (kg)	10.6 (1.3)	9.7 (1.3)	18.8 (8.5)	16.4 (6.4)
BSA (m^2)	0.46 (0.04)	0.44 (0.06)	0.78 (0.24)	0.70 (0.20)
Mood (a:c)	7:2	5:4	4:8	1:10*

TABLE II. *Measured and derived haemodynamic variables before induction (mean (*SEM*)). Group I = less than 2 yr, propofol; group II = less than 2 yr, thiopentone; group III = 2–12 yr, propofol; group IV = 2–12 yr, thiopentone. SAP = Systolic, DAP = diastolic, MAP = mean arterial pressures; HR = heart rate; SVI = stroke volume index; CI = cardiac index; SVR = systemic vascular resistance.* **P < *0.01*; ***P < *0.001*

	Group I ($n = 9$)	Group II ($n = 9$)	Group III ($n = 12$)	Group IV ($n = 11$)
SAP (mm Hg)	104.6 (5.3)	104.6 (5.3)	106.7 (5.0)	96.3 (3.9)
DAP (mm Hg)	71.6 (3.6)	70.4 (4.6)	67.9 (3.0)	61.2 (3.3)
MAP (mm Hg)	85.7 (3.4)	85.3 (5.0)	85.3 (3.8)	75.5 (2.9)
HR (beat min^{-1})	162.0 (12.3)	143.7 (10.1)	101.1 (5.7)	102.5 (4.2)***
SVI (ml $beat^{-1}$ m^{-2})	33.5 (3.8)	34.1 (2.5)	41.7 (1.6)	43.9 (3.8)
CI (litre min^{-1} m^{-2})	5.2 (0.5)	4.9 (0.5)	4.2 (0.2)	4.6 (0.3)
SVR (dyn s cm^{-5})	3129.7 (332.9)	3413.7 (289.6)	2290.6 (186.1)	2203.6 (226.9)**

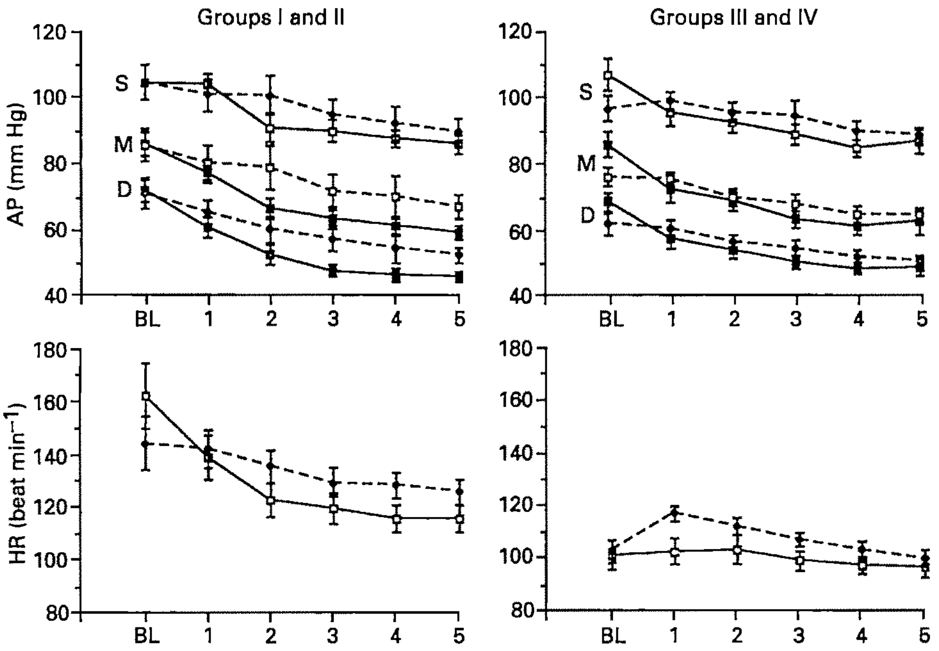


FIG. 1. Cardiovascular responses (HR = heart rate; AP = arterial pressure) during induction of anaesthesia in the children younger than 2 yr (groups I and II) and children aged 2–12 yr (groups III and IV). BL = Baseline (before induction); Time = time after induction; S = systolic pressure; M = mean arterial pressure; D = diastolic pressure. —— = Propofol; – – – = thiopentone.

older children (groups III and IV). The differences in arterial pressures, systemic vascular resistance and cardiac index among the four groups were not statistically significant.

After induction, systolic, mean and diastolic arterial pressures decreased significantly ($P < 0.001$) in all four groups (fig. 1). In the toddlers, the maximum reduction in mean arterial pressure was 31% after propofol (group I) and 21% after thiopentone (group II). In the older children, the maximum reductions were 28% after propofol (group III) and 14% after thiopentone (group IV). For both age groups, the differences were significantly more after propofol than after thiopentone ($P = 0.011$).

Heart rate decreased significantly in toddlers who received propofol (24%); the decrease was significantly more than for those who received thiopentone (11%) ($P = 0.024$). The mean heart rate was stable in the older children who received either propofol

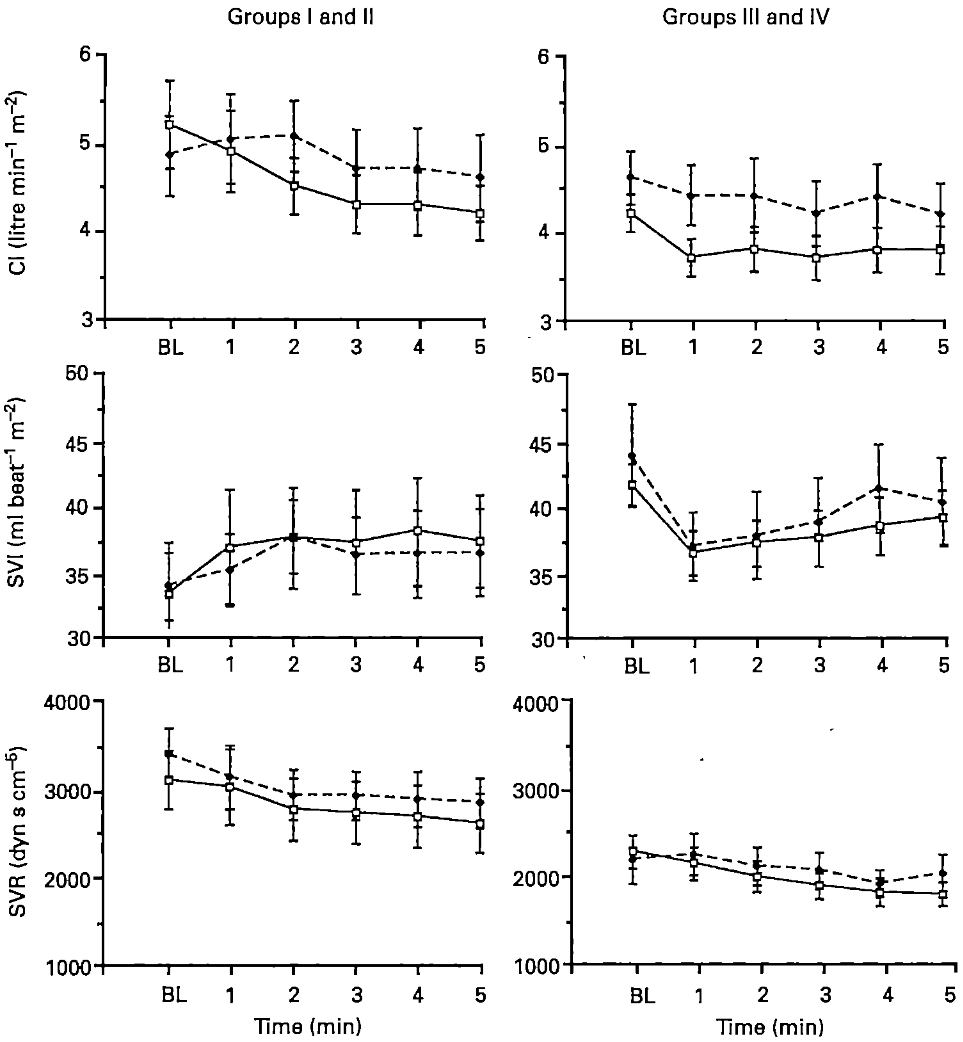


FIG. 2. Cardiovascular responses during induction of anaesthesia in the children younger than 2 yr (groups I and II) and children aged 2–12 yr (groups III and IV). BL = Baseline (before induction); Time = time after induction. CI = Cardiac index; SVI = stroke volume index; SVR = systemic vascular resistance. ——— = Propofol; – – – = thiopentone.

TABLE III. *Incidence of side effects at induction.* *P < 0.05

	Group I ($n = 9$)	Group II ($n = 9$)	Group III ($n = 12$)	Group IV ($n = 11$)
Pain on injection	2	0	4	1
Apnoea > 20 s	5	5	7	5
Movements	1	2	1	0

(group III) or thiopentone (group IV) (fig. 1). There was a significant difference ($P < 0.001$) in the magnitude of heart rate changes for the two age groups.

There was an increase in stroke volume index after induction up to a maximum of 12% in the toddlers both after propofol (group I) and after thiopentone (group II). In the older children, stroke volume index decreased maximally by 13% after propofol (group III) and 15% after thiopentone (group IV). These changes were not statistically different (fig. 2).

Cardiac index, which is a reflection of the combined effects of heart rate and systemic vascular resistance, decreased significantly ($P = 0.005$) in all four groups (fig. 2). In the toddlers, the maximum decrease in cardiac index was 15% after propofol and 3% after thiopentone. In the older children, the maximum reduction was similar (10%) after each agent.

Systemic vascular resistance decreased significantly ($P = 0.001$) after induction in all four groups (fig. 2). The maximum reduction was similar for the toddlers who received propofol (15%) and those who received thiopentone (16%). The decrease in systemic vascular resistance in older children who received propofol was almost three times as much (19%) as the reduction in children after thiopentone (7%). The differences between the four groups were not significant.

None of the children showed signs of wakening during the study period. There were no differences between the groups in the incidence of side effects (table III).

DISCUSSION

We have shown that i.v. induction of anaesthesia in children using propofol was associated with more cardiovascular depression than an equipotent dose (see below) of thiopentone. The degree of cardiovascular depression in toddlers was similar to that in older children.

This study used the non-invasive technique of pulsed Doppler and two-dimensional echocardiography to determine the stroke volume and cardiac output. The measurements are highly reproducible [11, 15] and can accurately detect relative cardiac output changes in individual patients. It has been shown to correlate well with thermodilution and dye dilution outputs in infants and young children [12, 15, 16]. Determination of cardiac output using M-mode echocardiography calculates volume from a measurement in a single dimension, and therefore any error made during the measurement could be magnified in the subsequent calculations [17]. M-mode identifies the aortic root area only during valve motion, whereas two-dimensional echocardiography can identify both aortic annulus (orifice) and root area. Aortic annulus diameter does not change during systole and therefore calculation of cardiac output using measurement at this site agrees more closely with invasive techniques than using aortic root measurements. Pulsed Doppler has been suggested to be a better technique than continuous Doppler. Pulsed Doppler permits measurement of flow velocity by range-gating at the specified location of the aortic orifice, whereas continuous wave Doppler measures velocity along the entire beam path and may include an area with a parabolic velocity profile which may give a misleading mean spatial velocity [12].

Equipotent doses are required for comparison of cardiovascular responses between two agents. We chose the dose of thiopentone 5 mg kg^{-1} as being equipotent with propofol 2.5 mg kg^{-1}. This ratio was based on previous work on their relative potencies [18, 19].

To our knowledge, no previous study has compared in children the cardiovascular effects of propofol and thiopentone during induction of anaesthesia. In this study we found that mean arterial pressure reduction after propofol was significantly greater than after thiopentone in both toddlers and older children ($P = 0.011$). This is similar to the finding in adults that propofol is more depressant on the cardiovascular system than thiopentone [2, 4]. Our magnitude of arterial pressure reduction after propofol was similar to that found in previous studies [7, 20, 21].

In healthy adults, thiopentone characteristically produces a reduction in arterial pressure and cardiac output, with or without a compensatory increase in total systemic vascular resistance [22–24] and a decrease in baroreflex sensitivity, associated with tachycardia [25]. The cardiovascular depression caused by thiopentone is caused by a combination of depression of the vasomotor centre [26] and direct myocardial depression [27, 28]. Venodilatation leading to a sequestration of blood volume in the venous side of the circulation and a reduction in the left ventricular diastolic filling and stroke volume have also been suggested [29]. The effect on arterial resistance vessels is variable as demonstrated by the inconsistent changes in systemic vascular resistance with barbiturates.

The children receiving thiopentone in our study had a significant reduction in arterial pressure and cardiac index. However, systemic vascular resistance decreased rather than increased. The changes in heart rate were different between the two age groups. Mean heart rate increased in the older children, but decreased in the toddlers (fig. 1). A comparative study of thiopentone in infants and children, observed a greater degree of myocardial depression than that in the present study [30], probably because of the larger dose of thiopentone (7.5–8.5 mg kg^{-1}) in that study.

Studies of the mechanism of propofol-induced hypotension in adults have produced conflicting results [31]. Lippmann and colleagues, using the thermodilution technique, observed a reduction in left ventricle stroke work index (35 %) and cardiac index (18 %), with no significant decrease in systemic vascular resistance and pulmonary vascular resistance [4]. Gauss and co-workers, using echocardiographic assessment and end-systolic quotient as an indicator of inotropy, found that propofol induced hypotension as a result of simultaneous negative inotropy and reduction in afterload [32]. Grounds and colleagues, using the thermodilution technique, observed a significant decrease in total systemic vascular resistance (18 %) with minimal changes in heart rate and cardiac output [2].

In this study, the magnitude of hypotension after propofol was similar to that found in adults [2]. It was associated with a significant reduction in both cardiac index (10–15 %) and systemic vascular resistance (15–19 %). Heart rate in the older children did not change, but it decreased significantly in the toddlers (fig. 1). More toddlers were crying on arrival in the operating theatre than among older children and this may have caused an increase in sympathetic tone. We suspect this was reflected in their greater heart rates and systemic vascular resistance. Anaesthesia attenuates sympathetic tone and this may have contributed to the greater reduction in heart rate in the toddlers. However, heart rates were all within the physiological range (fig. 2). Baroreceptor reflexes have been found to be more attenuated in both young animals and humans anaesthetized with halothane [33, 34] or nitrous oxide [35] compared with adults. It is possible, therefore, that the difference in reduction in heart rate was a reflection of a more significant baroreceptor impairment in the toddlers than in the older children. When comparing the two agents, the decrease in heart rate after propofol was greater than after thiopentone. This suggests that propofol causes more baroreflex depression than thiopentone, in agreement with previous studies in adult patients [36, 37].

Paediatric patients are thought to have a limited ability to increase myocardial contractility and heart rate is an important factor in determining cardiac output [38]. However, the toddlers in this study had an increase rather than a decrease in stroke volume index associated with the reduction in heart rate. This suggests that the myocardium is capable of increasing stroke volume in this age group. Ventricular diastolic filling time and stroke volume are inversely proportional to baroreceptor reflex-mediated changes in heart rate. The net effect of these haemodynamic responses was to produce a non-significant difference in the reduction of cardiac index in all four groups. Like thiopentone, there was no compensatory increase in systemic vascular resistance after propofol.

Diazepam premedication was necessary to reduce anxiety and allow baseline haemodynamic measurements. We used a dose of 0.4 mg kg^{-1} because, with smaller doses, excitement may occur from a lack of inhibition [39]. Its use as premedication is not associated with significant cardiovascular depression [40]. Any incidental haemodynamic effects caused by the premedication should be considered as relevant to the use of these induction agents in the clinical setting.

ACKNOWLEDGEMENT

We wish to thank Dr D. Y. H. Leung, the Faculty Statistician for his assistance with the statistical analysis of the data.

REFERENCES

1. Fahy LT, van Mourik GA, Utting JE. A comparison of the induction characteristics of thiopentone and propofol (2,6-di-isopropyl phenol). *Anaesthesia* 1985; **40**: 939–944.
2. Grounds RM, Twigley AJ, Carli F, Whitwam JG, Morgan M. The haemodynamic effects of intravenous induction, comparison of the effects of thiopentone and propofol. *Anaesthesia* 1985; **40**: 735–740.
3. McCollum JSC, Dundee JW. Comparison of induction characteristics of four intravenous anaesthetic agents. *Anaesthesia* 1986; **41**: 995–1000.
4. Lippmann M, Paicius RM, Gingerich S, Owens R, Mok MS, Appel P. A controlled study of the hemodynamic effects of propofol versus thiopentone during anesthesia induction. *Seminars in Anesthesia* 1988; 7 (Suppl. 1): 116–122.
5. Purcell-Jones G, Yates A, Baker JR, James IG. Comparison of the induction characteristics of thiopentone and propofol in children. *British Journal of Anaesthesia* 1987; **59**: 1431–1436.
6. Valtonen M, Iisalo E, Kanto J, Tikkanen J. Comparison between propofol and thiopentone for induction of anaesthesia in children. *Anaesthesia* 1988; **43**: 696–699.
7. Morton NS, Wee M, Christie G, Gray IG, Grant IS. Propofol for induction of anaesthesia in children. A comparison with thiopentone and halothane inhalational induction. *Anaesthesia* 1988; **43**: 350–355.
8. Monk CR, Coates DP, Prys-Roberts C, Turtle MJ, Spelina K. Haemodynamic effects of a prolonged infusion of propofol as a supplement to nitrous oxide anaesthesia. Studies in association with peripheral arterial surgery. *British Journal of Anaesthesia* 1987; **59**: 954–960.
9. Claeys MA, Gepts E, Camu F. Haemodynamic changes during anaesthesia induced and maintained with propofol. *British Journal of Anaesthesia* 1988; **60**: 3–9.
10. Wolf WJ, Neal MB, Peterson MD. The hemodynamic and cardiovascular effects of isoflurane and halothane anesthesia in children. *Anesthesiology* 1986; **64**: 328–333.
11. Alverson DC, Eldridge M, Dillon T, Yabek SM, Berman W. Noninvasive pulsed Doppler determination of cardiac output in neonates and children. *Journal of Pediatrics* 1982; **101**: 46–50.
12. Tibballs J, Osborne A, Hockmann M. A comparative study of cardiac output measurement by dye dilution and pulsed Doppler ultrasound. *Anaesthesia and Intensive Care* 1988; **16**: 272–277.
13. *Documenta Geigy*, 7th Edn. Basle: Ciba-Geigy, 1970; 538.
14. Kaplan JA. Hemodynamic monitoring. In: Kaplan JA, ed. *Cardiac Anesthesia*, 2nd Edn. Philadelphia: W. B. Saunders, 1987; 179–225.
15. Rein AJT, Hsieh KS, Elixson M, Colan SD, Lang P, Sanders SP, Castaneda AR. Cardiac output estimates in the pediatric intensive care unit using a continuous-wave Doppler computer: validation and limitations of the technique. *American Heart Journal* 1986; **112**: 97–103.
16. Mellander M, Sabel K-G, Caidahl K, Solymar L, Eriksson B. Doppler determination of cardiac output in infants and children: Comparison with simultaneous thermodilution. *Pediatric Cardiology* 1987; **8**: 241–246.
17. Slavik JR. Perioperative echocardiography. *Anesthesiology Clinics of North America* 1988; **6**: 769–783.
18. Grounds RM, Moore M, Morgan M. The relative potencies of thiopentone and propofol. *European Journal of Anaesthesiology* 1986; **3**: 11–17.
19. Leslie K, Crankshaw DP. Potency of propofol for loss of consciousness after a single dose. *British Journal of Anaesthesia* 1990; **64**: 734–736.
20. Short SM, Aun CST. Haemodynamic effects of propofol in children. *Anaesthesia* 1991; **46**: 783–785.
21. Hannallah RS, Baker SB, Casey W, McGill WA, Broadman LM, Norden JM. Propofol: effective dose and induction characteristics in unpremedicated children. *Anesthesiology* 1991; **74**: 217–219.
22. Elder JD, Nagano SM, Eastwood DW, Hagnagel D. Circulatory changes associated with thiopental anesthesia in man. *Anesthesiology* 1955; **16**: 394–400.
23. Flickinger H, Fraimow W, Cathcart RT, Nealon TF. Effect of thiopental induction on cardiac output in man. *Anesthesia and Analgesia* 1961; **40**: 693–700.
24. Etsten B, Li TH. Hemodynamic changes during thiopental anesthesia in humans: cardiac output, stroke volume, total peripheral resistance and intrathoracic blood volume. *Journal of Clinical Investigation* 1955; **34**: 500–510.
25. Britow JD, Prys-Roberts C, Fisher A, Pickering TG, Sleight P. Effects of anesthesia on baroreflex control of heart rate in man. *Anesthesiology* 1969; **31**: 422–428.
26. Skovsted P, Price ML, Price HL. The effects of short acting barbiturates on arterial pressure, preganglionic sympathetic activity and barostatic reflexes. *Anesthesiology* 1970; **33**: 10–18.
27. Conway CM, Ellis DB. The haemodynamic effects of short acting barbiturates. *British Journal of Anaesthesia* 1969; **41**: 534–542.
28. Sonntag H, Hellberg K, Schenk HD, Donath U, Regensburger D, Kettler D, Duchanova H, Larsen R. Effects of thiopental (Trapanal) on coronary blood flow and myocardial metabolism in man. *Acta Anaesthesiologica Scandinavica* 1975; **19**: 69–78.
29. Eckstein JW, Hamilton WK, McCammond JM. The effect of thiopental on peripheral venous tone. *Anesthesiology* 1961; **22**: 525–528.
30. Tibballs J, Malbezin S. Cardiovascular responses to induction of anaesthesia with thiopentone and suxamethonium in infants and children. *Anaesthesia and Intensive Care* 1988; **16**: 278–284.
31. Lippmann M, Boer F, Ros P, Bovill JG, Brummelen PV, Van Der Krogt J. Propofol: effect on the myocardium compared with the peripheral vascular system. *British Journal of Anaesthesia* 1991; **66**: 416–417.
32. Gauss A, Heinrich H, Wilder-Smith OHG. Echocardiographic assessment of the haemodynamic effects of propofol: a comparison with etomidate and thiopentone. *Anaesthesia* 1991; **46**: 99–105.
33. Wear R, Robinson S, Gregory GA. The effect of halothane on the baroresponse of adult and baby rabbits. *Anesthesiology* 1980; **56**: 188–191.
34. Gregory GA. The baroresponses of preterm infants during halothane anaesthesia. *Canadian Anaesthesia Society Journal* 1982; **29**: 105–107.

35. Duncan PG, Gregory GA, Wade JG. The effect of nitrous oxide on baroreceptor function in newborn and adult rabbits. *Canadian Anaesthesia Society Journal* 1981; **28**: 339–341.
36. Cullen PM, Turtle M, Prys-Roberts C, Way WL. Effects of propofol anesthesia on baroreflex activity in humans. *Anesthesia and Analgesia* 1987; **66**: 1115–1120.
37. Ebert TJ, Muzi M, Berens R, Goff D, Kampine JP. Sympathetic responses to induction of anesthesia in humans with propofol or etomidate. *Anesthesiology* 1992; **76**: 725–733.
38. Robinson S. Cardiovascular physiology in pediatrics. In: Gregory GA, ed. *Pediatric Anesthesia*, 1st Edn. New York: Churchill Livingstone, 1983; 9–33.
39. Kosarussavadi B. Premedication. In: Bell C, Hugues CW, Oh TH, eds. *The Pediatric Anesthesia Handbook*. St Louis: Mosby Year Book, 1991; 71–80.
40. Fell D, Gough MB, Northan AA, Henderson CU. Diazepam premedication in children, plasma levels and clinical effects. *Anaesthesia* 1985; **40**: 12–17.

British Journal of Anaesthesia 1993; **70**: 654–660

EFFECT OF EXTRADURAL ANALGESIA ON STRESS RESPONSES TO ABDOMINAL SURGERY IN INFANTS†

A. R. WOLF, R. L. EYRES, P. C. LAUSSEN, J. EDWARDS, I. J. STANLEY, P. ROWE AND L. SIMON

SUMMARY

We studied 40 children younger than 4 yr having elective abdominal surgery under general anaesthesia supplemented with either systemic opioids or extradural bupivacaine. Venous blood samples were obtained before tracheal intubation to measure baseline concentrations of adrenaline, noradrenaline, glucose, ACTH and cortisol. Additional samples were obtained 45 min after the start of surgery, at the end of surgery, 1 h and 24 h after the end of surgery. Plasma concentrations of bupivacaine were measured also in the extradural group at each sampling time. Both techniques provided acceptable analgesia, but the perioperative increases in adrenaline, glucose and ACTH were significantly greater in the opioid group. Noradrenaline concentrations decreased to less than baseline values in the extradural group and were significantly less than in the opioid group. The perioperative increase in cortisol was similar in the two groups, despite the differences in ACTH responses. Most responses returned to the baseline values within 24 h. Plasma bupivacaine concentrations remained within safe limits during the study, but systemic concentrations increased in some of the patients during postoperative infusion with 0.125% bupivacaine. (Br. J. Anaesth. 1993; **70**: 654–660)

KEY WORDS

Anaesthesia: paediatric. Anaesthetic techniques: extradural, caudal. Metabolism: stress response.

Studies on newborn infants have demonstrated that inadequate analgesia or anaesthesia may result in a massive stress response and that analgesic drugs which modify the response can be beneficial to postoperative recovery [1, 2]. Unfortunately, effective ablation of the stress response to major surgery requires doses of opioids far greater than are needed to provide analgesia, and necessitates postoperative ventilation [3]. This is impractical for most infant surgery and opioids are limited usually to doses which allow immediate postoperative extubation.

In adults, extradural bupivacaine can suppress stress responses to pelvic and lower limb surgery more effectively than conventional analgesic doses of systemic opioids [4, 5]. However, responses to upper abdominal surgery remain marked even when analgesic combinations of extradural bupivacaine, systemic morphine and indomethacin are used [6]. In children, lumbar extradural and caudal blocks with local anaesthetics can abolish or reduce the increase in cortisol and catecholamines in response to inguinal herniorrhaphy, orchidopexy and hypospadias repair [7, 8], but there are no data on the effect of extradural techniques on stress responses in infants undergoing major abdominal surgery.

We have measured the blood concentrations of adrenaline, noradrenaline, glucose, ACTH and cortisol in infants having abdominal surgery under general anaesthesia supplemented with either extradural bupivacaine or systemic opioids. We hypothesized that extradural analgesia would suppress stress responses to abdominal surgery to a greater extent than opioid analgesia even when both groups received dosage adequate to produce postoperative analgesia.

PATIENTS AND METHODS

The investigation was approved by the Ethics Committee at the Royal Children's Hospital in Melbourne. Informed parental consent was obtained to study 40 infants younger than 4 yr, undergoing elective abdominal surgery. Patients with known endocrine or neurological abnormalities and those with conditions likely to alter stress hormones (such as pain or hypovolaemia) were excluded from study.

Patients older than 4 months received premedication with trimeprazine syrup 1.5 mg kg^{-1} 1 h before surgery. On arrival in the operating room, baseline arterial pressure and heart rate were measured. Anaesthesia was induced with nitrous oxide and halothane in oxygen, and an i.v. cannula was inserted to obtain baseline blood samples before intubation. The cannula was heparinized and remained dedicated for subsequent venous blood

---

ANDREW R. WOLF, M.A., M.B., B.CHIR., F.R.C.ANAES., The Royal Hospital for Sick Children, Yorkhill, Glasgow G3 8SJ. ROBERT L. EYRES, M.B., F.F.A.R.A.C.S.; PETER C. LAUSSEN, M.B., F.F.A.R.A.C.S; JOSIANE EDWARDS, B.SC.; The Royal Hospital for Sick Children, Melbourne, Australia. IRENE J. STANLEY, PH.D., Department of Endocrinology, Royal Melbourne Hospital, Australia. PETER ROWE, DIP.APPL.SC., Department of Clinical Pharmacology, The Austin Hospital, Melbourne, Australia. LAURA SIMON, M.A., Department of Biostatistics, Penn State University, Hershey, Pennsylvania, U.S.A. Accepted for Publication: December 9, 1992.

Correspondence to A.R.W.

†Presented in part at the Annual Meeting of the American Society of Anesthesiology, San Francisco, October 1991.

samples. Vecuronium was given via a second i.v. cannula placed in another limb, to facilitate tracheal intubation. Fluid maintenance comprised Ringer's lactate solution in a standardized fashion (4 ml kg^{-1} h^{-1} for subjects weighing up to 10 kg and an additional 2 ml kg^{-1} h^{-1} in those heavier than 10 kg). Additional losses were replaced with Ringer's lactate or blood products according to clinical requirements. Anaesthesia was maintained with 70 % nitrous oxide and 0.5–1 % halothane in oxygen. Arterial pressure and heart rate were recorded at 5-min intervals throughout surgery.

Patients were allocated randomly to receive either i.v. opioids or extradural bupivacaine during and after surgery. Patients in the opioid group were given fentanyl 1 μg kg^{-1} before surgical incision. Additional doses of 0.5 μg kg^{-1} were administered if systolic arterial pressure or heart rate increased to 20 % greater than baseline. Halothane concentration was increased temporarily to a maximum of 1 % during episodes of hypertension and tachycardia while the fentanyl was taking effect. Patients in the extradural group were turned on their side and an extradural cannula was inserted via either the caudal or lumbar route according to clinical preference, using a Portex minipack system (ref: 100/391/091) which provides a 22-gauge extradural catheter. The catheters were inserted in a rostral direction to a distance calculated to leave the tip at a position appropriate for the proposed surgery (the upper lumbar region for lower abdominal surgery and the mid thoracic region for upper abdominal surgery). An initial dose of 0.25 % plain bupivacaine 1 ml was given after insertion of the catheter, and subsequent dosing with 0.25 % bupivacaine was based on the same haemodynamic criteria as for the fentanyl group. The total volume was limited to 1 ml kg^{-1} (bupivacaine 2.5 mg kg^{-1}) during surgery to avoid systemic overdosing.

After surgery, the patients remained in a recovery area for 1 h before discharge to the regular ward. Nursing staff evaluated pain in the recovery area, and on the ward, using a simple scoring system: 0 = asleep; 1 = no pain (awake and calm); 2 = mild pain (crying but able to be comforted); 3 = moderate to severe pain requiring additional analgesia (agitated, crying and not able to be comforted). Morphine was used for postoperative analgesia in the opioid group and nursing staff were allowed to administer a loading dose of morphine 10–50 μg kg^{-1}, to ensure that each patient had adequate analgesia (pain scores of 0, 1 or 2) in the recovery area. An infusion was commenced at an initial rate of 10–20 μg kg^{-1} h^{-1}, and modified up to a maximum of 50 μg kg^{-1} h^{-1} according to 4-hourly pain observations. Incremental doses of 50 μg kg^{-1} were also permitted as necessary to maintain good analgesia. Smaller infants who were sedated after surgery were not given a morphine infusion in the recovery area but prescribed "as required" doses of morphine 25–50 μg kg^{-1} on the ward.

An infusion of 0.125 % bupivacaine was given for postoperative analgesia to patients in the extradural group, at an initial rate of 0.2 ml kg^{-1} h^{-1}, increased to a maximum of 0.3 ml kg^{-1} h^{-1} if analgesia appeared inadequate. Additional doses of 0.125 % or 0.25 % bupivacaine were given by anaesthesia personnel in the recovery area or on the ward at the request of the recovery or ward nursing staff. No formal attempt was made to evaluate the dermatomal levels of the extradural block during the study because of the unreliability of such measurement in this age group. The total dose of bupivacaine given to any child was limited to less than 1.6 mg kg^{-1} in any 4-h period (0.4 mg kg^{-1} h^{-1}) to avoid the risks of systemic accumulation and toxicity.

A 2.5-ml venous blood sample was taken after induction of anaesthesia, but before tracheal intubation for measurement of baseline adrenaline, noradrenaline, glucose, ACTH and cortisol concentrations. Subsequent samples were obtained 45 min after the start of surgery, at the end of surgery, 1 h and 24 h after surgery. All samples were placed immediately on ice. Samples for catecholamine assay (1.5 ml) were collected into heparinized tubes on ice, centrifuged at 4 °C and the plasma stored at −70 °C until assay by high pressure liquid chromatography (HPLC) and electrochemical detection after prior extraction with alumina [9]. Coefficients of variation for the adrenaline and noradrenaline assays were 6–11 % at 0.5 ng ml^{-1} and 3–5 % at 1 ng ml^{-1}, respectively. The limits of detection were 45 pg ml^{-1} for adrenaline and 30 pg ml^{-1} for noradrenaline. Whole blood glucose was measured by enzymatic technique (glucose oxidase). ACTH samples (200-μl) were kept in EDTA tubes and centrifuged at 4 °C within 1 h of collection. The plasma was stored at −70 °C and measured for ACTH concentration using a highly specific radioimmunoassay (Allegra HS-ACTH, Nichols Institute Diagnostics). Quality controls for the technique had coefficients of variation of 9.4 % at 3.5–6.4 nmol $litre^{-1}$, 6.4 % at 17–22 nmol $litre^{-1}$ and 3.9 % at 90–133 nmol $litre^{-1}$ and the lower limit of sensitivity of the assay was 3.3 nmol $litre^{-1}$. Cortisol samples (0.5 ml) were measured from serum by radioimmunoassay (Diagnostic Products Corporation's Double Antibody Kit). The assay is highly specific with a coefficient of variation of 5.9 % at 180 nmol $litre^{-1}$ and 7.9 % at 1260 nmol $litre^{-1}$. The lower limit of sensitivity is 9 nmol $litre^{-1}$. In addition, plasma bupivacaine was measured in samples from patients in the extradural group. The technique used an HPLC method [10] with a coefficient of variation for extraction of less than 5 % and a coefficient of variation for measurement of 2.86 % at 1 μg ml^{-1} and 2.12 % at 2 μg ml^{-1}.

Changes in the plasma concentrations of adrenaline, noradrenaline, ACTH and cortisol were evaluated via log transformation. The log transformation was used to reduce the skewness of the data in order to meet the assumptions of the statistical method used. Repeated measures analyses were used to model and test differences in each of the log responses. Time, treatment and their interaction were considered potential explanatory factors in the variation of the mean log responses. Preliminary evaluation of the correlation structures of each of the log responses suggested that the assumptions of equal variances and equal correlations were satisfied

[11]. Therefore, the *F* tests for a standard split-plot analysis were used to test for significant time and treatment effects. For this analysis, only times coinciding with treatment, namely 45 min, end of surgery and recovery, were included. Then, to determine if the log responses at 24 h returned to baseline values, paired *t* tests were performed on pretreatment and post-treatment values. In this study, the different hormonal and metabolic responses are correlated because they are measured on the same subjects and some adjustment for multiple comparisons might be indicated. However, the statistical resolution between groups is sufficiently large that the results are not affected by a variety of adjustments. The *P* values are reported in the unadjusted state. The paired *t* tests on pretreatment and post-treatment values are also not adjusted for multiple comparisons; here, because we were trying to "prove" the null hypothesis.

RESULTS

Patients in the opioid and extradural groups were similar in age, weight and type of surgical procedures (table I). The average duration of surgery was 99.7 (SD 50.4) min in the opioid group and 111.0 (47.9) min in the extradural group.

Intraoperative arterial pressure and heart rate remained within 20% of baseline values in both groups. The average systolic arterial pressure was 99.3 (12.8) mm Hg in the opioid group and 94.6 (15.6) mm Hg in the extradural group. The averaged heart rates were 131.0 (20.1) beat min^{-1} in the opioid group and 123.5 (19.4) beat min^{-1} in the extradural group. The average dose of fentanyl given during operation was 1.34 (0.6) $\mu\text{g kg}^{-1}\text{ h}^{-1}$. Fourteen of the 20 patients in the opioid group were judged as pain-free in the recovery room and the remaining six settled rapidly after a loading dose of morphine. A mean dose of bupivacaine 20.2 (9.2) $\mu\text{g kg}^{-1}\text{ h}^{-1}$ was given during surgery to control haemodynamic changes. Two patients in the extradural group were judged to be in pain in recovery and both settled after a 0.5-ml kg^{-1} injection of 0.25% bupivacaine (1.25 mg kg^{-1}). Restlessness and agitation were reported in six extradural patients on the ward, but these were treated satisfactorily with incremental doses of extradural bupivacaine. Four patients in each group were given supplementary paracetamol for pyrexia or pain.

Plasma adrenaline concentrations (fig. 1) increased significantly from baseline values by 45 min after the start of surgery in both groups (paired *t* tests, $P < 0.001$). In the opioid group, the adrenaline concentrations had returned to baseline values by 24 h (paired *t* test, $P = 0.65$), while in the extradural group they remained slightly increased at 24 h (paired *t* test, $P = 0.03$). Patients in the extradural group had significantly smaller concentrations of adrenaline than the opioid group (*F* test, $P = 0.005$).

Plasma noradrenaline concentrations (fig. 2) did not change significantly during or after surgery in the opioid group but, in the extradural group, concentrations decreased during surgery and were significantly less than those in the opioid group (*F* test, $P = 0.03$). The noradrenaline concentrations at baseline and 24 h were not significantly different for the opioid or extradural group (paired *t* tests, $P = 0.22$ and $P = 0.67$, respectively).

Baseline concentrations of blood glucose were within normal limits: the smallest values were 2.5 mmol litre^{-1} in the opioid group and 2.4 mmol

TABLE I. *Patient data (mean (range or SD)) and details of surgery*

	Opioid analgesia	Extradural analgesia
Age (yr)	1.2 (0.2–4.0)	1.5 (0.2–3.9)
Weight (kg)	9.9 (5.4)	10.4 (3.9)
Operations	($n = 20$)	($n = 20$)
Reimplantation ureters	6	7
Laparotomy	5	3
Renal pyeloplasty	4	4
Total nephrectomy	—	2
Partial nephrectomy	1	2
Colonic "pull through"	1	1
Closure ectopic bladder	1	1
Vesicostomy	1	—
Closure colostomy	1	—

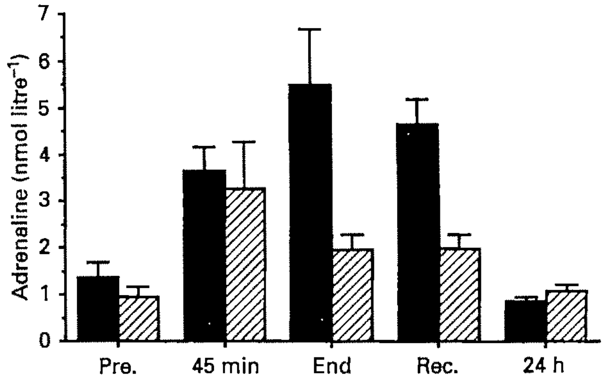


FIG. 1. Comparison of plasma adrenaline concentrations from patients receiving systemic opioid analgesia (■) or extradural bupivacaine analgesia (▨) before surgery (Pre.), 45 min after the start of surgery, at the end of surgery (End), 1 h after surgery (Rec.) and 24 h after surgery (means, SE). Adrenaline concentrations were significantly different in the two treatment groups (*F* test, $P = 0.005$).

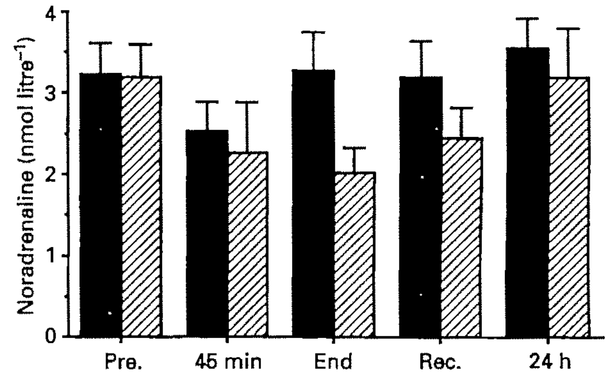


FIG. 2. Comparison of plasma noradrenaline concentrations from patients receiving systemic opioid analgesia (■) or extradural bupivacaine analgesia (▨) before surgery (Pre.), 45 min after the start of surgery, at the end of surgery (End), 1 h after surgery (Rec.) and 24 h after surgery (means, SE). Noradrenaline concentrations were significantly different in the two treatment groups (*F* test, $P = 0.03$).

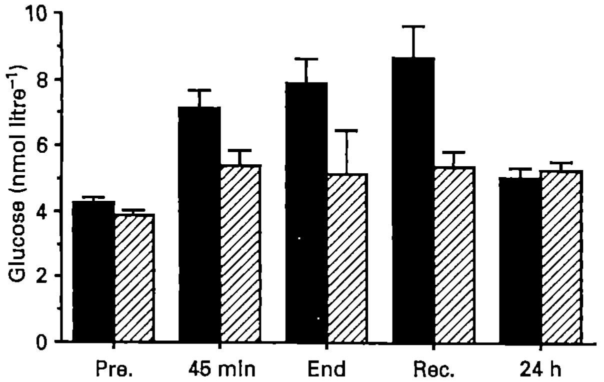


FIG. 3. Comparison of blood glucose concentrations from patients receiving systemic opioid analgesia (■) or extradural bupivacaine analgesia (▨) before surgery (Pre.), 45 min after the start of surgery, at the end of surgery (End), 1 h after surgery (Rec.) and 24 h after surgery (means, SE). Glucose concentrations were significantly different in the two treatment groups (*F* test, $P = 0.004$).

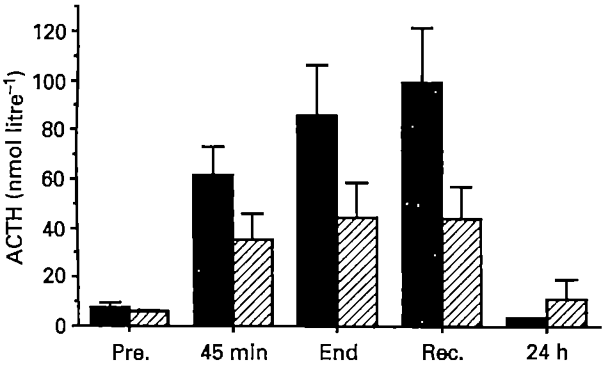


FIG. 4. Comparison of plasma ACTH concentrations from patients receiving systemic opioid analgesia (■) or extradural bupivacaine analgesia (▨) before surgery (Pre.), 45 min after the start of surgery, at the end of surgery (End), 1 h after surgery (Rec.) and 24 h after surgery (means, SE). ACTH concentrations were significantly different in the two treatment groups (*F* test, $P = 0.008$).

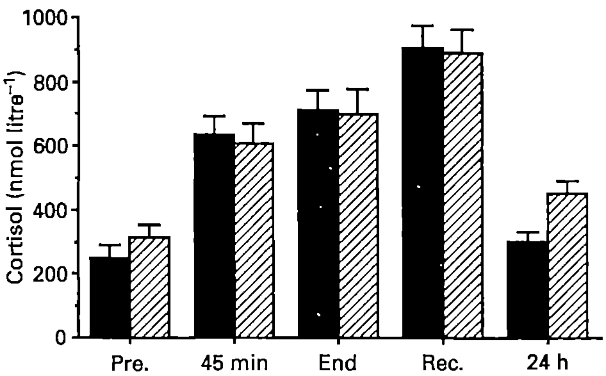


FIG. 5. Comparison of plasma cortisol concentrations from patients receiving systemic opioid analgesia (■) or extradural bupivacaine analgesia (▨) before surgery (Pre.), 45 min after the start of surgery, at the end of surgery (End), 1 h after surgery (Rec.) and 24 h after surgery (means, SE). There was no significant difference between the two treatment groups (*F* test, $P = 0.56$).

litre^{-1} in the extradural group. Whole blood glucose concentrations increased in both treatment groups during surgery (fig. 3), but were significantly greater in the opioid group (*F* test, $P = 0.004$). Blood glucose

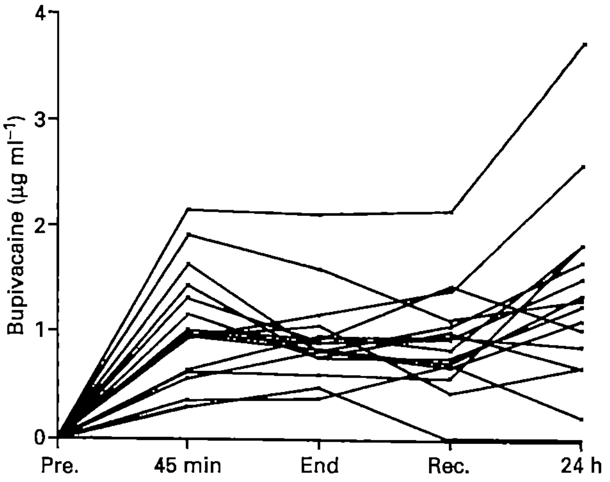


FIG. 6. Patient-by-patient display of plasma bupivacaine concentrations at 45 min after the start of surgery, at the end of surgery (End), 1 h after surgery (Rec.) and at 24 h after surgery.

concentrations remained greater than baseline in both groups at 24 h (opioid group: $P = 0.02$; extradural group: $P = 0.001$). Four patients in the morphine group and three in the extradural group required blood transfusion during the 24-h study period, and this may have contributed to the increase in blood glucose in those children.

ACTH concentrations (fig. 4) increased in both groups during surgery (paired *t* tests, $P < 0.001$), but the response was significantly greater in the opioid group (*F* test, $P = 0.008$). The 24-h concentrations were significantly different from baseline in the opioid group (paired *t* test, $P = 0.01$), but similar to baseline in the extradural group (paired *t* test, $P = 0.47$).

Plasma cortisol concentrations (fig. 5) increased significantly with surgery in both groups (paired *t* tests, $P < 0.001$), but the group-related differences in ACTH concentrations were not reflected in the associated plasma cortisol results (*F* test, $P = 0.56$). Power analysis indicated that the power of the test to detect a difference in the means of log cortisol of 0.1 between the two treatment groups was approximately 90%. Cortisol concentrations remained greater than baseline at 24 h after surgery in the extradural group (paired *t* test, $P = 0.004$), but not in the opioid group (paired *t* test, $P = 0.25$).

Individual plasma concentrations of bupivacaine are shown in figure 6. Postoperative infusions were not associated with increasing bupivacaine concentrations when analysed as a group, but there was large individual variation. Two patients had bupivacaine concentrations that increased to more than 2 µg ml^{-1} during the postoperative infusion, but no unusual behaviour was reported in those patients by the nursing staff. The patient attaining a 24-h value of 3.7 µg ml^{-1} was an 8.3-kg child who received a total of 25 mg of bupivacaine (3 mg kg^{-1}) during a 2-h procedure. The postoperative infusion delivered 0.3 ml kg^{-1} h^{-1} of 0.125% bupivacaine (0.375 mg kg^{-1} h^{-1}) and a single bolus of 2.5 mg was given at 16 h. These doses were just greater than designated guidelines for the study. The second patient weighed 10 kg and received bupivacaine 20 mg (2 mg kg^{-1})

during the 85-min procedure and had an infusion of 0.25 ml kg^{-1} h^{-1} (0.3 mg kg^{-1} h^{-1}) after surgery without further incremental bupivacaine. This patient was given a bupivacaine dosage well inside the guidelines for this study.

All patients entered into the trial completed the operative and recovery phases. Two patients in the bupivacaine group had to be changed to i.v. morphine analgesia in the postoperative period. The first patient, reported previously in detail [12], developed signs of an ascending block while receiving the postoperative infusion. Subarachnoid block, hypoglycaemia and bupivacaine toxicity were excluded from the diagnosis and the child had an uneventful recovery after the infusion had been discontinued. The second patient had to be transferred to a morphine infusion after the extradural cannula fell out 16 h after operation. Both these patients remained in the study, but their 24-h samples were excluded from analysis. In the morphine group, one patient was changed to pethidine analgesia because of urticaria and facial swelling and another required a second laparotomy at 26 h for bleeding after a Ladd's procedure. The 24-h blood samples from these patients were also excluded from the study.

DISCUSSION

General anaesthesia supplemented with either opioids or extradural local anaesthesia provides comparable postoperative analgesia [13]. However, in this study we have shown that extradural analgesia with 0.25% bupivacaine suppressed the operative increase in adrenaline, glucose and ACTH more effectively than fentanyl 1.3 μg kg^{-1} h^{-1}. Noradrenaline output was reduced by extradural analgesia, but the cortisol changes in the two groups were similar despite the different ACTH responses. We have used anaesthetic techniques that are compatible with routine clinical practice: opioid dosing that allowed immediate postoperative tracheal extubation with adequate postoperative analgesia, and intraoperative extradural dosing based on simple changes in heart rate and arterial pressure, rather than attaining a specific level of block before surgery.

While there are considerable adult data on the effects of anaesthesia on stress responses to surgery, data in infants are limited. Recent neonatal studies [1–3] for cardiac and non-cardiac surgery are not easy to compare with the present study: many of the neonates had abnormal baseline measurements because of preoperative stress or therapy [3] and data were presented subsequently as changes in variables rather than absolute values. We specifically chose elective procedures, and efforts were made to eliminate preoperative stresses at induction of anaesthesia by using premedication, gaseous induction and avoidance of parental separation when appropriate. The resulting preoperative values were within normal limits and allowed a subsequent analysis using absolute values. The study could have been further improved by limiting the investigation to a single intra-abdominal procedure. This was not done for practical reasons of patient availability, but the two groups were matched for operation type and duration of surgery. Nursing staff evaluating pain were aware of the group assignment and pain observations were used to guide analgesia management, not to compare the quality of analgesia formally. Blinding the observers to the type of analgesia used is possible [13], but confers additional complexity and we did not deem it necessary in this study.

Extradural anaesthesia may eliminate the increase in catecholamine concentrations in response to pelvic surgery in adults [4] and caudal bupivacaine has a similar effect [8] in children undergoing minor urogenital surgery. The effects of extradural analgesia on intra-abdominal surgery are less clear [14], but studies which have documented high levels of sensory block before abdominal incision are associated with some reduction in the adrenaline response and substantial reductions or even abolition of the noradrenaline response [15, 16]. The catecholamine responses after extradural analgesia in the present study are in keeping with this adult data. Extradural analgesia *per se* from T4 to T10 has no effects on adrenaline concentrations, but results in a decrease in noradrenaline concentration because of reduction in sympathetic outflow [17]. Although we were unable to document levels of conduction block before surgical incision, the reduction in noradrenaline response during surgery suggests that our infants had conduction blocks high enough to block splanchnic innervation.

Peak adrenaline concentrations in the opioid group were greater than those in adult studies [4, 15, 16], but similar to those in neonates undergoing cardiac surgery with a morphine–halothane technique [3]. Adrenaline concentrations had diminished by 1 h after surgery and were close to baseline values within 24 h. This is in contrast with adults in whom catecholamine concentrations continue to increase after surgery [4, 15, 16] and supports the view that stress responses in infants are greater in magnitude but of shorter duration than those in adults [18].

Changes in concentrations of catabolic hormones, such as adrenaline and cortisol, during surgery result in glycogenolysis and hyperglycaemia. The glucose responses in the present study are similar to adult data in abdominal and thoracic surgery [19], which have shown that extradural analgesia has a significant blocking effect. Neonatal studies of non-cardiac [1, 2] and prebypass cardiac surgery [3] have reported much larger increases in blood glucose concentrations, even in those patients who received large doses of sufentanil. However, baseline blood glucose concentrations were increased before operation and it is difficult to compare directly absolute values of glucose with previous studies because of the influence of perioperative glucose infusions on subsequent measurements [20]. We chose to avoid glucose infusions during surgery to eliminate this effect, but the postoperative use of glucose-containing solutions has affected our 24-h samples.

The greater ACTH concentrations in the opioid group did not induce an increased cortisol response. In adults, extradural analgesia can reduce ACTH and cortisol responses to lower abdominal surgery, but has little or no effect on the cortisol response to upper abdominal surgery [19]. In children also, extradural analgesia can suppress the cortisol response to minor lower limb and penile surgery [7], but there has not previously been any data on responses to abdominal surgery. Upper abdominal or thoracic surgery is a more potent stimulus to the stress response than more minor surgery and it has been claimed that this stimulus is sufficient to produce a maximal or near maximal response from the adrenal cortex [21, 22]. This view is supported by the observation that ACTH response to surgery is often in excess of that required to produce maximal cortical response [22], and that administration of exogenous ACTH during surgery is unable to elicit further increases in cortisol [23]. In the present study, the peak cortisol values of 906.8 (313.5) nmol litre^{-1} in the opioid group and 891.1 (332.0) nmol litre^{-1} in the extradural group are similar to the greatest values recorded in adult patients having abdominal or cardiac surgery regardless of anaesthetic technique [5, 24, 25]. Therefore, the smaller concentrations of ACTH in the extradural group may still have been sufficient to produce a maximal cortisol response. Certainly, the concentrations of cortisol are greater than those seen in previous paediatric studies [1, 2, 7, 26] and are equivalent to the greatest values observed in a group of neonates (non-survivors) undergoing cardiac surgery [27]. Other possible explanations for these observations should be considered. Extradural analgesia may influence the blood supply to the adrenal cortex or an alternative humoral mechanism may independently stimulate cortisol production. Several of the cytokines can stimulate the adrenocortical axis and these are produced at high levels during abdominal surgery [28].

Recent case reports of convulsions from systemic bupivacaine absorption have highlighted the potentially hazardous nature of continuous bupivacaine infusions in small children [29, 30]. All the five reported cases received large doses of bupivacaine in excess of 1.25 mg kg^{-1} h^{-1} and had concentrations greater than 5 μg ml^{-1}. Recommendations to limit dose rates to 0.4–0.5 mg kg^{-1} in infants and children and to 0.2–0.25 mg kg^{-1} in neonates [31] are reasonable, but do not necessarily prevent systemic accumulation. In the present study we limited the intraoperative dose to 2.5 mg kg^{-1} (0.25% bupivacaine 1 ml kg^{-1}) and the postoperative dose to 0.4 mg kg^{-1} h^{-1} (0.125% bupivacaine 0.3 ml kg^{-1} h^{-1} with bolus doses of 0.125% or 0.25% bupivacaine). These doses are well inside the recently recommended guidelines [31], and the majority of the patients had small concentrations of bupivacaine throughout the study. However, while there was no significant postoperative increase in bupivacaine concentrations for the group as a whole, there was considerable variability. Two of the patients did accumulate relatively large concentrations from the bupivacaine infusion (fig. 6), and it is likely that the concentrations would have continued to increase after 24 h [30]. It is essential, therefore, to remain alert for the signs of bupivacaine toxicity even when "safe" guidelines are used.

ACKNOWLEDGEMENTS

This study was supported by funding from the Department of Anaesthesia at The Royal Children's Hospital, Melbourne, Australia. We thank Dr Kester Brown for his support and suggestions.

REFERENCES

1. Anand KJS, Sippell WG, Aynsley-Green A. Randomised trial of fentanyl anaesthesia in preterm babies undergoing surgery: effects on the stress response. *Lancet* 1987; **1**: 243–248.
2. Anand KJS, Sippell WG, Schofield NM, Aynsley-Green A. Does halothane anaesthesia decrease the metabolic and endocrine stress responses of newborn infants undergoing operation? *British Medical Journal* 1988; **296**: 668–672.
3. Anand KJS, Hickey PR. Halothane–morphine compared with high-dose sufentanil for anesthesia and postoperative analgesia in neonatal cardiac surgery. *New England Journal of Medicine* 1992; **326**: 1–9.
4. Engquist A, Fog-Moller F, Christiansen C, Thode J, Vester-Anderson T, Madsen SN. Influence of epidural analgesia on the catecholamine and cyclic AMP responses to surgery. *Acta Anaesthesiologica Scandinavica* 1980; **24**: 17–21.
5. Engquist A, Mogens R, Fernandes A, Kehlet H. The blocking effect of epidural analgesia on the adrenocortical and hyperglycaemic responses to surgery. *Acta Anaesthesiologica Scandinavica* 1977; **21**: 330–335.
6. Schulze S, Roikjaer O, Hasselstrom L, Jensen NH, Kehlet H. Epidural bupivacaine and morphine plus systemic indomethacin eliminates pain but not systemic response and convalescence after cholecystectomy. *Surgery* 1988; **103**: 321–327.
7. Murat I, Walker J, Esteve C, Nahoul K, Saint-Maurice C. Effect of lumbar epidural anaesthesia on plasma cortisol levels in children. *Canadian Journal of Anaesthesia* 1988; **35**: 20–24.
8. Dupont D, Velin P, Cabour F, Candito M, Rives E. Influence de l'anesthésie caudale sur la secretion des catecholamines chez l'enfant. *Annales Françaises d'Anesthésie et de Réanimation* 1987; **6**: 156–158.
9. Salzman SK, Sellers MS, Beckman AL, Naidu R, Macewen GD. Determination of intraoperative plasma catecholamine concentrations using liquid chromatography with electrochemical detection. *Journal of Chromatography* 1985; **343**: 285–301.
10. Eyres RL, Hastings C, Brown TCK, Oppenheim RC. Plasma bupivacaine concentrations following lumbar epidural anaesthesia in children. *Anaesthesia and Intensive Care* 1986; **14**: 131–134.
11. Milliken GA, Johnson DE. *Analysis of Messy Data, Vol. 1: Designed Experiments.* New York: Van Nostrand Reinhold, 1984.
12. Wolf AR, Walker SM. Development of a high block in an infant during an epidural bupivacaine infusion. *Anaesthesia and Intensive Care* 1991; **19**: 583–585.
13. Wolf AR, Hughes D. Pain relief for infants undergoing abdominal surgery: comparison of infusions of i.v. morphine and extradural bupivacaine. *British Journal of Anaesthesia* 1993; **70**: 10–16.
14. Hjortso NC, Christensen NJ, Andersen T, Kehlet H. Effects of the extradural administration of local anaesthetic agents and morphine on the urinary excretion of cortisol, catecholamines and nitrogen following abdominal surgery. *British Journal of Anaesthesia* 1985; **57**: 400–406.
15. Rutberg H, Hakanson E, Anderberg B, Jorfeldt L, Martensson J, Schildt B. Effects of the extradural administration of morphine or bupivacaine on the endocrine response to upper abdominal surgery. *British Journal of Anaesthesia* 1984; **56**: 233–237.
16. Tonnesen E, Huttel MS, Christensen NJ, Schmitz O. Natural killer cell activity in patients undergoing upper abdominal surgery: relationship to the endocrine stress response. *Acta Anaesthesiologica Scandinavica* 1984; **28**: 654–660.
17. Ecoffey C, Edouard A, Pruszczynski W, Taly E, Samii K. Effects of epidural anesthesia on catecholamines, renin activity, and vasopressin changes induced by tilt in elderly men. *Anesthesiology* 1985; **62**: 294–297.
18. Anand KJS. Hormonal and metabolic functions of neonates

and infants undergoing surgery. *Current Opinion in Cardiology* 1986; 1: 681–689.

19. Kehlet H. Modification of response to surgery by neural blockade: clinical implications. In: Cousins MJ, Bridenbaugh PO, eds. *Neutral Blockade*, 2nd Edn. Philadelphia: J. B. Lippincott Company, 1988; 145–188.
20. Welborn LG, McGill WA, Hannallah RS, Nisselson CL, Ruttiman UE, Hicks JM. Perioperative blood glucose concentrations in pediatric outpatients. *Anesthesiology* 1986; 65: 543–547.
21. Traynor C, Hall GM. Endocrine and metabolic changes during surgery: anaesthetic implications. *British Journal of Anaesthesia* 1981; 53: 153–160.
22. Oyama T, Wakayama S. The endocrine responses to general anesthesia. *International Anesthesiology Clinics* 1988; 26: 176–186.
23. Thoren L. General metabolic response to trauma including pain influence. *Acta Anaesthesiologica Scandinavica (Supplementum)* 1974; 55: 9–14.
24. Moller IW, Hjortso E, Krantz T, Wandall E, Kehlet H. The modifying effect of spinal anaesthesia on intra- and postoperative adrenocortical and hyperglycaemic responses to surgery. *Acta Anaesthesiologica Scandinavica* 1984; 28: 266–269.
25. Walsh ES, Paterson JL, O'Riordan JBA, Hall GM. Effect of high dose fentanyl anaesthesia on the metabolic and endocrine response to cardiac surgery. *British Journal of Anaesthesia* 1981; 53: 1155–1165.
26. Sigurdsson G, Lindahl S, Norden N. Influence of premedication on plasma ACTH and cortisol concentrations in children during adenoidectomy. *British Journal of Anaesthesia* 1982; 54: 1075–1080.
27. Anand KJS, Hansen DD, Hickey PR. Hormonal–metabolic stress responses in neonates undergoing cardiac surgery. *Anesthesiology* 1990; 73: 661–670.
28. Naito Y, Tamai S, Shingu K, Shindo K, Matsui T, Segawa H, Nakai Y, Mori K. Responses of plasma adrenocorticotrophic hormone, cortisol, and cytokines during and after upper abdominal surgery. *Anesthesiology* 1992; 77: 426–431.
29. Agarwal R, Gutlove DP, Lockhart CH. Seizures occurring in pediatric patients receiving continuous infusion of bupivacaine. *Anesthesia and Analgesia* 1992; 75: 284–286.
30. McCloskey JJ, Haun SE, Deshpande JK. Bupivacaine toxicity secondary to continuous caudal epidural infusion in children. *Anesthesia and Analgesia* 1992; 75: 287–290.
31. Berde C. Convulsions associated with pediatric regional anesthesia. *Anesthesia and Analgesia* 1992; 75: 164–166.

British Journal of Anaesthesia 1993; 70: 661–665

VOLUME REPLACEMENT WITH HYDROXYETHYL STARCH SOLUTION IN CHILDREN

J. BOLDT, C. KNOTHE, E. SCHINDLER, H. HAMMERMANN, F. DAPPER AND G. HEMPELMANN

SUMMARY

In 30 consecutive children undergoing cardiac surgery, two different types of fluid were given randomly for volume replacement in the pre-bypass period. In group 1 (n = 15), low molecular weight hydroxyethyl starch solution (LMW-HES) (6% HES; mean molecular weight 200000 Da, molar substitution 0.5) and in group 2 (n = 15) 20% albumin (HA) was infused from the induction of anaesthesia until the start of cardiopulmonary bypass (CPB). In addition to haemodynamic values, various laboratory variables were measured before and after CPB until the morning of the 1st day after operation. The patients did not differ in diagnosis and conduct of CPB (lowest rectal temperatures: group 1 29.0 (SD 1.1)°C; group 2 29.4 (1.0)°C). Haemodynamic data (MAP, HR, CVP), anti-thrombin-III, fibrinogen, platelet count and coagulation variables were comparable between the groups until the 1st day after operation. Postoperative blood loss and the use of homologous blood or blood products were similar in all children. Albumin concentration increased after infusion of albumin (35–47 g litre^{-1}) and was significantly greater until the end of the operation compared with the LMW-HES-treated children. Colloid osmotic pressure, however, was similar in the two groups and returned to baseline values on the 1st day after operation (LMW-HES group 19.31 (1.2) mm Hg; HA group 18.0 (1.3) mm Hg). Post-bypass urine output and creatinine values also did not differ between the groups. Anaphylactic reactions were not observed in any of the patients. It can be concluded that LMW-HES solution can be used effectively and safely for volume replacement in the pre-bypass period in small children undergoing cardiac surgery. (Br. J. Anaesth. 1993; **70**: 661–665)

KEY WORDS

Anaesthesia: paediatric. Fluid balance: albumin, hydroxyethyl starch.

A proportion of children undergoing cardiac surgery need volume expansion in the pre-bypass period because of the vasodilator effects of the anaesthetics or surgical blood loss. A variety of fluids is recommended to enhance blood volume and improve haemodynamics in this situation, including homologous blood and blood products, crystalloids and albumin [1–3]. Albumin appears to be the fluid used most frequently for volume therapy in paediatric cardiac surgery. In contrast, in adults, synthetic colloids such as hydroxyethyl starch solution (HES) are used to treat volume deficits in various situations, including cardiac surgery procedures [4]. In several centres, HES has replaced albumin as the first choice for volume replacement. However, experience with HES for volume therapy in children is limited. The aim of this study was to establish if HES could be used safely for volume replacement in children undergoing cardiac surgery.

PATIENTS AND METHODS

We studied 30 consecutive children aged less than 3 yr and undergoing cardiac surgery, after approval by the institutional review board and with informed parental consent. Children undergoing reoperation or with pre-existing coagulation or renal abnormalities, or a haemoglobin (Hb) concentration less than 10 g dl^{-1} were excluded. Hypovolaemia was defined as a reduced central venous pressure (CVP) (< 6 mm Hg), ventilation-associated variations in arterial pressure, increase in heart rate or a decrease in arterial pressure (mean arterial pressure (MAP) < 50 mm Hg). Volume replacement was given after induction of anaesthesia until the start of cardiopulmonary bypass (CPB). According to a randomized sequence, either low molecular weight hydroxyethyl starch solution (LMW-HES) (6% HES; mean molecular weight 200000 Da; molar substitution 0.5) (LMW-HES Fresenius; Bad Homberg, F.R.G.) (*n* = 15) or 20% human albumin (HA) (HA, Behring, Marburg, F.R.G.) (*n* = 15) was given to achieve a stable haemodynamic state. All volume infusion was requested by anaesthetists who were not involved in the study and who were blinded to the volume given.

J. Boldt, M.D., C. Knothe, M.D., E. Schindler, M.D., H. Hammermann, M.D., G. Hempelmann, M.D. (Department of Anaesthesiology and Intensive Care Medicine); F. Dapper, M.D. (Department of Cardiovascular Surgery); Klinikstr. 29, Justus-Liebig-University Giessen, D-6300 Giessen, Germany. Accepted for Publication, December 24, 1992.

TABLE I. *Patient data and perioperative data (mean* (SD) *[range]). CPB = Cardiopulmonary bypass; Ischaemia = period of aortic cross-clamping; RBC (packed red cells) and FFP (fresh frozen plasma) were given in the postbypass period until the 1st day after operation.* $^{*}P < 0.05$

	LMW-HES group	Albumin group
Age (month)	11.2 [1–30]	10.0 [1–24]
Weight (kg)	8.2 (3.3) [3.0–12.1]	7.7 (3.2) [4.3–12.1]
Infused volume		
(ml)	106 (11) [70–180]	67 (22) [30–120]*
(ml kg^{-1})	12.1 (3.4) [7.5–15.0]	8.5 (2.8) [5.3–10.2]*
Duration of CPB (min)	129 (21) [116–189]	119 (23) [96–169]
Duration of ischaemia (min)	74 (14) [60–100]	67 (20) [42–100]
Lowest rectal temp. (°C)	29.0 (1.1) [28.1–32.0]	29.4 (1.0) [28.0–33.0]
Fluid balance during CPB (ml)	+80 (70) [−100 to +150]	+120 (50) [+100 to +200]
Total volume given (ml)		
RBC	1050	990
FFP	1450	1390
Platelets	660	550

Anaesthesia and cardiopulmonary bypass (CPB)

Induction and maintenance of anaesthesia were comparable in both groups and consisted of weight-related doses of fentanyl, midazolam and pancuronium. Controlled mechanical ventilation ($F\text{I}_{O_2}$, ventilation frequency and volume) was adjusted according to pulse oximetry (Sp_{O_2}), end-expiratory carbon dioxide concentration and blood-gas analyses.

Five minutes before CPB, heparin 300 u. kg^{-1} was given to achieve anticoagulation. CPB was performed with membrane oxygenators (COBE VPCMLplus, Cobe Lab., Lakewood, Colorado, U.S.A.) and non-pulsatile perfusion (flow 2.4 litre min^{-1} m^{2}). Lowest rectal temperatures were similar between groups (LMW-HES 29.0 (1.1)°C; HA 29.4 (1.0)°C). Hypothermic cardiocirculatory arrest was not used. The extracorporeal circuit was primed with crystalloids 600 ml and 5% human albumin 250 ml. When necessary to maintain the pump volume, Ringer's solution was added. Packed red cells (RBC) were given when Hb was < 7 g dl^{-1}. Bretschneider's cardioplegic solution was used for myocardial preservation. After successful weaning from CPB, protamine was given in a 1:1 ratio with respect to the initial amount of heparin. Blood remaining in the extracorporeal oxygenation equipment was concentrated by a cell saver (Cell Saver III, Haemonetics, Munich, F.R.G.) and the autologous blood was retransfused until the end of the operation. The same surgical team operated on all patients.

Measured variables

Besides haemodynamic monitoring (heart rate (HR), mean arterial pressure (MAP), central venous pressure (CVP)), various laboratory values were measured from arterial blood samples: blood-gas analyses, colloid osmotic pressure (COP) (cut-off point of the membrane 20000 Da), electrolytes, fibrinogen, anti-thrombin-III, albumin, platelet count, overall coagulation tests. Measurements were made before volume infusion (baseline values), immediately before the start of CPB, during and after CPB, at the end of the operation, 5 h after the operation and on the morning of the 1st day after operation.

After operation, RBC were given when Hb was < 10 g dl^{-1}, fresh frozen plasma was given when bleeding exceeded 5 ml kg^{-1} h^{-1} and platelet count was > 50000 ml^{-1} (activated clotting time (ACT) < 200 s), platelet concentrates were administered when bleeding exceeded 5 ml kg^{-1} h^{-1} and platelet count was < 50000 ml^{-1} (ACT < 200 s). All volume therapy within the study period was given by paediatric intensive care specialists who were blinded to the grouping.

Statistics

Power analysis had been done before the study was started, to determine the number of patients which would be necessary to prevent a type II error in the statistical interpretation. All data are expressed as mean (SD). One- and two-factorial analyses of variance (including multivariate analysis of variance followed by Scheffé's test) were used for statistical interpretation. Chi-square test was used to analyse

TABLE II. *Operative procedures in the two groups*

	LMW-HES group ($n = 15$)	Albumin group ($n = 15$)
Atrio-ventricular canal repair	2	2
Tetralogy of fallot repair	4	4
Atrial septum and ventricular septum defect repair	4	3
Aorto-pulmonary shunt	3	3
Kawasaki syndrome	1	1
Truncus arteriosus	1	—
Pulmonary stenosis and atrial septum defect repair	—	2

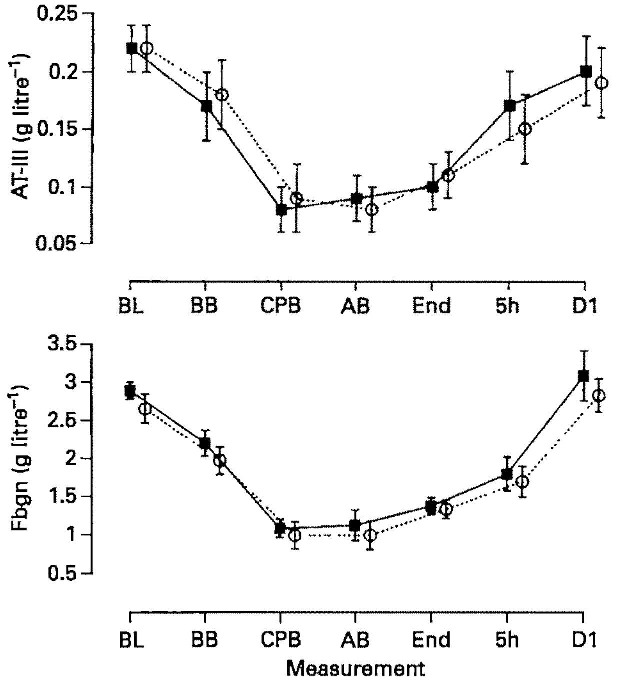


FIG. 1. Mean (SD) changes in anti-thrombin-III (AT-III) and fibrinogen (Fbgn) concentrations in the hydroxyethyl starch (○) and human albumin (■) groups (normal ranges: AT-III 0.15–0.30 g litre^{-1}; fibrinogen 2.0–3.5 g litre^{-1}). BL = Baseline; BB = before CPB; CPB = during CPB; AB = after CPB; End = end of operation; 5h = 5 h after operation; D1 = 1st day after operation.

differences for homologous blood use. $P < 0.05$ was considered to be significant.

RESULTS

Patient data, conduct of CPB (table I) and type of operation (table II) were comparable in both groups. Total volumes of LMW-HES 106 (11) ml and albumin 67 (22) ml were given in the pre-bypass period ($P < 0.05$). Fluid balance during CPB was also without group differences (table I).

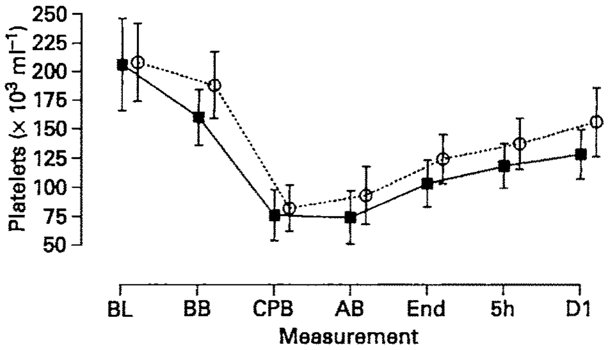


FIG. 2. Mean (SD) changes in platelet count in the hydroxyethyl starch (○) and human albumin (■) groups. Key to measurements as in figure 1.

Haemodynamic data (MAP, HR, CVP) in both groups showed a comparable course throughout (table III). Anti-thrombin III, fibrinogen and platelet count did not differ between the groups (fig. 1); neither did the general coagulation variables (thrombin time, partial thromboplastin time) and platelet count (fig. 2).

Plasma albumin concentration increased after infusion of 20% HA and was significantly greater until the end of the operation (fig. 3). COP, however, was similar between groups and recovered to baseline values on the 1st day after operation (fig. 3). Serum electrolytes and creatinine concentrations and postoperative blood loss were also comparable between groups (table III). In the HES group, urine output was significantly smaller during the bypass period, but was similar to that in the HA group in the remainder of the study (table III).

Postoperative blood loss until the 1st day after operation was comparable in the two groups (LMW-HES 27 (12) ml kg^{-1}; HA 25 (11) ml kg^{-1}) (table III). Total use of homologous blood, fresh frozen plasma and platelet concentrates was similar in both groups (table I).

None of the children had any signs of anaphylaxis during infusion of LMW-HES, or suffered sequelae attributable to the study.

TABLE III. *Mean* (SD) *changes in mean arterial pressure* (*MAP*), *heart rate* (*HR*) *and central venous pressure* (*CVP*), *and cumulative urine output and blood loss in the postbypass period until the 1st day after operation* (*1st day*) *in the two groups.* *$P < 0.05$

	Baseline	Before CPB	During CPB	After CPB	End of operation	5 h after operation	1st day
MAP (mm Hg)							
LMW-HES	59 (4)	67 (4)	58 (5)	62 (5)	68 (5)	70 (4)	71 (5)
Albumin	60 (4)	66 (3)	52 (2)	69 (4)	71 (3)	72 (5)	72 (4)
HR (beat min^{-1})							
LMW-HES	154 (18)	139 (24)	—	141 (20)	144 (23)	149 (19)	148 (21)
Albumin	149 (21)	150 (22)	—	150 (23)	151 (21)	152 (22)	154 (19)
CVP (mm Hg)							
LMW-HES	4 (2)	9 (2)	—	9 (3)	11 (3)	11 (2)	9 (2)
Albumin	4 (2)	9 (3)	—	11 (4)	12 (3)	10 (2)	8 (2)
Urine output (ml)							
LMW-HES	—	—	60 (20)	180 (40)	370 (80)	490 (80)	690 (120)
Albumin	—	—	140 (30)*	220 (60)	400 (100)	600 (120)	780 (110)
Creatinine (μmol litre^{-1})							
LMW-HES	—	—	—	—	—	85 (7)	93 (5)
Albumin	—	—	—	—	—	90 (6)	95 (3)
Blood loss (ml kg^{-1})							
LMW-HES	—	—	—	—	—	10 (8)	27 (12)
Albumin	—	—	—	—	—	11 (9)	25 (11)

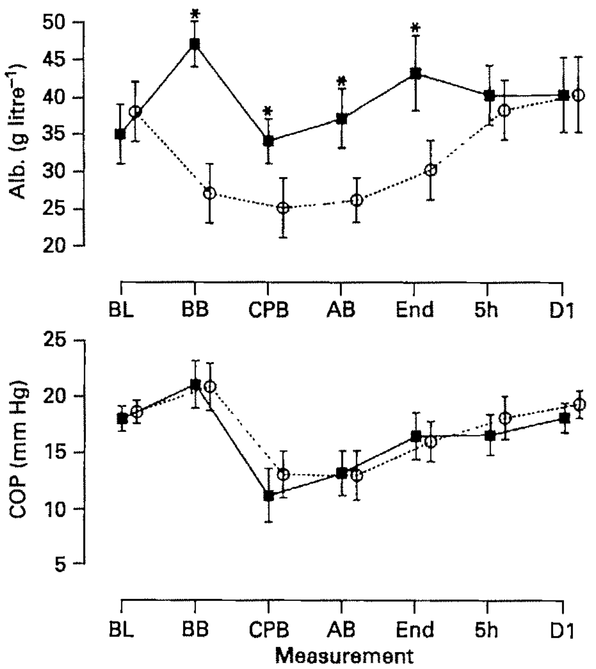


FIG. 3. Mean (SD) changes in albumin (Alb.) concentration and colloid osmotic pressure (COP) in the hydroxyethyl starch (○) and human albumin (■) groups (normal ranges: albumin 35–45 g litre^{-1}; COP 17–20 mm Hg). Key to measurements as in figure 1. *$P < 0.05$.

DISCUSSION

Replacement of fluid deficits is an essential aspect of cardiac surgery and is as important in the adult as in the infant or child. In the pre-bypass period, medication and blood loss may significantly alter the patient's blood or plasma volume [5]. One of the reasons for the use of albumin instead of crystalloids is the prevention of pulmonary oedema by augmenting colloid osmotic pressure. Thus maintenance of COP is postulated to be a desirable goal of volume replacement. Dilution of serum protein, particularly during CPB, decreases COP, which is associated with the risk of progressive expansion of the interstitial space. However, the effects of albumin depend on its movement between the intra- and extravascular compartments. This cannot be predicted because CPB may affect capillary permeability [6, 7]. Weaver and colleagues [8] have demonstrated that albumin molecules may extravasate into the interstitium and thus may favour fluid movement out of the capillaries because of their water binding capacity. In a study in critically ill adults comparing colloid infusions (5% albumin, Dextran and HES), there was a greater increase in extravascular lung water in the albumin group than in HES-treated patients [9]. In the present study, plasma concentrations of albumin were greater in the albumin-treated patients until the end of the operation than in the children receiving LMW-HES. COP, however, did not differ between groups. None of the children had signs of pulmonary oedema on the postoperative chest x-ray or progressive respiratory failure. Several studies of different plasma substitutes in adults have failed to show convincing differences between HES and albumin [10, 11]. The haemodynamic data obtained in the present study did not suggest any differences in the circulatory effects of the two solutions. Another objection to the use of HES solution for volume replacement in paediatric cardiac surgery may result from fear of alterations in coagulation. We used LMW-HES because it appears to have significantly less effect on haemostasis (and platelet function) than standard, high-molecular weight HES solution (6% HES 450000; molar substitution 0.7) [12, 13]. We did not observe any differences in coagulation factors between the two groups. Moreover, postoperative blood loss and use of blood or blood products were comparable in the two groups.

Changes in renal function may also be a reason for a limited use of synthetic colloids in this situation. In the present study, urine output and electrolytes were comparable in both groups, indicating comparable changes in renal function.

Possible accumulation of HES molecules in tissues, particularly in the reticulo-endothelial system, has often been an argument against the use of HES solutions in children. However, animal studies have not shown any changes in organ function as a result of storage of HES [14]. Moreover, LMW-HES appears less likely to cause tissue accumulation than other HES preparations [15]. Although "outcome" is not a good variable for assessing the importance of HES accumulation, none of our patients showed signs of organ dysfunction.

It is concluded that demonstration of the superiority of a particular fluid for volume replacement is difficult. However, LMW-HES has economic advantages in comparison with albumin solutions [16], and can be used safely in children undergoing cardiac surgery.

REFERENCES

1. Linko K, Mäkeläinen A. Cardiorespiratory function after replacement of blood loss with hydroxyethylstarch 120 dextran-70 and Ringer's acetate in pigs. *Critical Care Medicine* 1989; **17**: 1031–1035.
2. Lumb PD. A comparison between 25% albumin and 6% hydroxyethyl starch solution on lung water accumulation during and immediately after cardiopulmonary bypass. *Annals of Surgery* 1987; **206**: 210–215.
3. Stockwelll MA, Soni N, Riley B. Colloid solutions in the critically ill. *Anaesthesia* 1992; **47**: 3–6.
4. London ML. Plasma expansion in cardiovascular surgery: practical realities, theoretical concerns. *Journal of Cardiothoracic Anesthesia* 1988; **6** (Suppl. 1): 39–49.
5. Utley JR, Stephens DB. Fluid balance during cardiopulmonary bypass. In: Utley JR, ed. *Pathophysiology and Technique of Cardiopulmonary Bypass*, Vol. I. Baltimore: Williams & Wilkins, 1983; 23–33.
6. Royston D, Minty B, Higenbottom TW, Wallwork J. The effect of surgery with cardiopulmonary bypass on alveolar–capillary barrier function in human beings. *Annals of Thoracic Surgery* 1985; **40**: 139–144.
7. Kirklin JK, Blackstone EH, Kirklin JW. Cardiopulmonary bypass: studies on its damaging effects. *Blood Purification* 1987; **5**: 168–178.
8. Weaver DW, Ledgerwood AM, Lucas CE, Higgins R, Bouwman DL, Johnson SD. Pulmonary effects of albumin resuscitation for severe hypovolemic shock. *Archives of Surgery* 1978; **113**: 387–392.
9. Finch JS, Reid C, Bandy K, Kickle D. Compared effects of selected colloids on extravascular lung water in dogs after oleic acid induced lung injury and severe hemorrhage. *Critical Care Medicine* 1983; **11**: 267–270.

10. Paidipaty BB, Puri VK. Colloid infusion in patients with adult respiratory distress syndrome. *Critical Care Medicine* 1982; **10**: 16A.
11. Rackow EC, Falk JL, Fein IA, Siegel JS, Packmann MJ, Haupt MT, Kaufmann BS, Putma MD. Fluid resuscitation in circulatory shock: a comparison of the cardiorespiratory effects of albumin hetastarch and saline solutions in patients with hypovolemic and septic shock. *Critical Care Medicine* 1983; **11**: 839–850.
12. Strauss RG. Volume replacement and coagulation: a comparative review. *Journal of Cardiothoracic Anesthesia* 1988; **2** (Suppl. 1): 24–32.
13. Boldt J, Knothe C, Zickmann B, Andres P, Dapper F, Hempelmann G. Influence of different volume therapy on platelet function in patients undergoing cardiopulmonary bypass. *Anesthesia and Analgesia* 1993; (in press).
14. Mishler JM, Nicora RW, Yoshitake T, Oishe K, Kawasaki T, Shimizu K. Hemodilution with hydroxyethyl starch during cardiopulmonary bypass: review of a multi-institutional study. *American Society of Extracorporeal Circulation* 1975; **3**: 140–149.
15. Quon CY. Clinical pharmacokinetics and pharmacodynamics of colloid plasma volume expanders. *Journal of Cardiovascular Anesthesia* 1988; **2** (Suppl. 1): 13–23.
16. Davidson I. Fluid resuscitation of shock: current controversies. *Critical Care Medicine* 1989; **17**: 1078–1080.

British Journal of Anaesthesia 1993; 70: 666–671

PHARMACOKINETICS AND PHARMACODYNAMICS OF KETAMINE ENANTIOMERS IN SURGICAL PATIENTS USING A STEREOSELECTIVE ANALYTICAL METHOD†

G. GEISSLINGER, W. HERING, P. THOMANN, R. KNOLL, H.-D. KAMP AND K. BRUNE

SUMMARY

In a randomized, double-blind study, we have examined the stereoselective disposition and pharmacodynamic characteristics of ketamine in surgical patients after i.v. administration of S(+)*-ketamine 1 mg/kg body weight (25 patients) or racemic ketamine 2 mg/kg body weight (25 patients).* S(+)*-Ketamine was not inverted to* R(−)*-ketamine. After racemate administration we observed statistically significant (*$P < 0.01$*) smaller clearance and volume of distribution for* R(−)*-ketamine compared with* S(+)*-ketamine. In contrast, the pharmacokinetic variables of* S(+)*-ketamine were not significantly different between treatment groups. Systolic and diastolic arterial pressure and heart rate increased significantly (*$P < 0.005$*) in both groups. At 1, 3 and 15 min after* S(+)*-ketamine administration, significantly greater increase in systolic and diastolic pressures were observed compared with the racemate group. There was no correlation between the changes in haemodynamic variables and plasma catecholamine concentrations, which remained unaffected after administration of the medications.* (Br. J. Anaesth. 1993; **70**: 666–671)

KEY WORDS

Anaesthetics, intravenous: ketamine,. Pharmacodynamics: enantiomers. Pharmacokinetics.

The relevance of stereochemistry to drug action and disposition is well documented [1–4]. Ketamine ((±)-2-(o-chlorophenyl)-2-(methylamino)cyclohexanone hydrochloride) is a dissociative anaesthetic agent which has been in clinical use as a racemate for more than 20 years [5–7]. Its use is associated with sensory and perceptual illusions, and vivid dreams after anaesthesia ("emergence reactions") [5], although diazepam alleviates these psychic sequelae [8].

Studies with the ketamine enantiomers have suggested both quantitative and qualitative differences in their effects on the central nervous system [9–13]. White and colleagues reported differences in their anaesthetic potency, intraoperative effects, postoperative analgesia and side effects in surgical patients [14]. It has been concluded that the S(+)-enantiomer has four times the potency of the R(−)-enantiomer and it may have significant clinical advantages in comparison with the racemic drug [14, 15]. Some studies of the pharmacokinetics of ketamine have used the sole enantiomers [14–16], but the pharmacokinetic parameters of a chiral compound should be assessed using stereoselective analytical methods [2]. Therefore the present investigation was designed to examine pharmacokinetic characteristics stereoselectively and to compare the pharmacodynamics of S(+)-ketamine with the currently available racemate (Ketalar) in surgical patients. Recommended equi-anaesthetic doses of racemic ketamine (2 mg/kg body weight) and S(+)-ketamine (1 mg/kg body weight) were administered i.v. in a random, double-blind fashion [14]. It was possible also to scrutinize the hypothesis that elimination of racemic ketamine is stereoselective, as has been speculated previously [4].

MATERIALS AND METHODS

Reference compounds

The enantiomers of ketamine and norketamine were supplied by Gödecke AG (Freiburg, Germany), and had chemical and optical purities of greater than 98.5%. The ampoules containing S(+)-ketamine (28.83 mg ml^{-1} as the hydrochloride, equivalent to S(+)-ketamine 25 mg ml^{-1}, lot CF 078099) and racemic ketamine (57.67 mg ml^{-1} as the hydrochloride, equivalent to ketamine racemate 50 mg ml^{-1}, lot CF 083109) were also supplied by Gödecke AG.

Patients

We studied 50 adult patients (10 females), ASA physical status I or II, undergoing minor surgery

---

Gerd Geisslinger, ph.d., m.d.; Peter Thomann, m.sc.; Kay Brune, m.d.; Department of Experimental and Clinical Pharmacology and Toxicology, University of Erlangen–Nuernberg, Universitaetsstr. 22, D-8520 Erlangen, Germany. Werner Hering, m.d.; Rainer Knoll, m.sc.; Hans-Dieter Kamp, m.d.; Department of Anaesthesiology, Maximiliansplatz 1, University of Erlangen–Nuernberg, D-8520 Erlangen, Germany. Accepted for Publication: December 30, 1992.

Correspondence and reprint requests to G.G.

†Reported in part at the Annual Meeting of American Society of Anesthesiologists, October 17–21, 1992, New Orleans, U.S.A. (*Anesthesiology* 1992; 77: A331).

TABLE I. *Patient characteristics (No. (%) or mean (range)). Broca index = weight (kg)/(f × (height (cm) − 100)); f = 0.85 for females and 0.9 for males*

	S(+)-ketamine ($n = 25$)	Racemic ketamine ($n = 25$)
Sex		
Male	21 (84)	19 (76)
Female	4 (16)	6 (24)
Age (yr)	33 (18–58)	37 (18–59)
Broca index	1.16 (0.91–1.56)	1.14 (0.80–1.56)

lasting 1–2 h. The sample size was based on a power-based calculation of changes in systolic arterial pressure ($n = 22$ patients each group, 90 % power at a 5 % level on a two-sided t test). The usual exclusion criteria for ketamine anaesthesia were followed. The patients had no previous history or evidence of renal, hepatic, heart or pulmonary diseases, or of drug hypersensitivity. Smoking was not an exclusion criterion. Patients' characteristics are summarized in table I.

Study design

The study was approved by the University of Erlangen Medical Ethics Review Committee and written informed consent was obtained. Following enrolment in the study, patients were assigned in a random, double-blind fashion to one of two treatment groups by means of random permuted blocks of 10. One group ($n = 25$) received racemic ketamine, the second group ($n = 25$) S(+)-ketamine. In order to perform the study in a double-blind fashion, it was necessary to administer equal volumes of different concentrations of the two agents. The chemical composition of the enantiomer solution was identical to that of the commercially available product (Ketalar) except for the ketamine constituent.

Premedication comprised midazolam (Dormicum) 5 mg i.m. approximately 45 min before operation. A cannula was inserted into an antecubital vein in each arm and anaesthesia was induced with midazolam (Dormicum) 0.1 mg kg^{-1} i.v. over 30 s. Four minutes later, a single dose of ketamine 0.04 ml kg^{-1} was administered over 30 s, resulting in doses of S(+)-ketamine 1 mg kg^{-1} and racemic ketamine 2 mg kg^{-1}, respectively. Neuromuscular blocking drugs were used according to normal clinical practice. Four minutes after administration of ketamine the trachea was intubated. Ten minutes after ketamine administration, anaesthesia was maintained with nitrous oxide and 5 min later with nitrous oxide and enflurane. At the conclusion of the operation, enflurane and nitrous oxide were discontinued, residual neuromuscular block was antagonized and the trachea was extubated when clinically appropriate.

Haemodynamic effects

After arrival of the patient in the preoperative holding area and a rest of 10 min, the stable baseline systolic and diastolic arterial pressures and heart rate were measured using a Dinamap non-invasive monitor, followed by measurements at 2 min after midazolam was given and at 1, 3, 5, 7, 10 and 15 min after administration of ketamine.

Blood sampling and measurements of plasma catecholamines

Whole blood (4 ml) was obtained in cooled, heparinized tubes before administration of midazolam, 1 min before administration of ketamine and 3, 4, 5, 7, 10 and 15 min thereafter. The blood was cooled on ice for 10 min, and then centrifuged at 4 °C. Plasma (2 ml) was frozen and stored at −80 °C in tubes containing 40 µl of stabilizer (EGTA 9.5 g, glutathione 6.0 g, water 100 ml; Sigma Chemie, Deisenhofen, Germany) until analysis. Adrenaline and noradrenaline were measured using a slightly modified liquid chromatography assay with electrochemical detection as described previously [17]. The limit of quantification (the smallest concentration that could be determined during the inter-assay validation with either precision or accuracy of less than or equal to 15 %) was 20 pg ml^{-1} for both catecholamines. Quality control samples were included to verify the accuracy and precision of analysis. The samples were not stored longer than 3 weeks before analysis.

Collection of blood and analysis of ketamine enantiomers

Approximately 3 ml of heparinized blood was collected before and at 1, 3, 5, 7, 10, 15, 30 and 45 min and at 1.0, 1.5, 2.0, 3.0, 4.0, 6.0, 8.0, 10.0 and 12.0 h after administration of the ketamine bolus. The blood samples were centrifuged and the separated plasma stored at −30 °C with plasma quality control samples, pending analysis. The concentrations of ketamine and norketamine enantiomers were analysed by a high-pressure liquid chromatography method using a chiral alpha$_1$-acid glycoprotein column as described previously [18]. Separation was achieved without any derivatization procedure. One enantiomer of bisnortilidine (ethyl DL-trans-2-amino-1-phenyl-3-cyclohexane-1-carboxylate, as the hydrochloride) proved suitable as the internal standard. The detection wavelength was 215 nm for all substances. The retention times of the internal standard, S(+)-norketamine, S(+)-ketamine, R(−)-ketamine and R(−)-norketamine were about 14.5 min, 17.5 min, 25 min and 28 min, respectively. The separation factors for the chiral resolution of the enantiomers of ketamine and norketamine exceeded 1.15 and 1.75, respectively. The limit of quantification (the smallest concentration that could be measured during the inter-assay validation with either precision or accuracy of less than or equal to 15 %) was 40 ng/ml of plasma for ketamine and norketamine enantiomers. No reliance was placed on the detection limit (signal to noise ratio 3:1). Quality control samples were included to verify the accuracy and precision of stereoselective analysis.

Kinetic analysis of data

Non-compartmental pharmacokinetic variables [19] were calculated using the Topfit program package [20]. The terminal elimination rate constants (λ_z) were estimated by performing standard, unweighted linear least-squares regression analysis of the linear segment of the plasma log concentration–time data. The terminal elimination half-life ($T_{\frac{1}{2}}$) was calculated by dividing 0.693 by the absolute value of λ_z. The area under the drug concentration–time curve ($AUC_{0-\infty}$) was estimated by the linear and log-linear trapezoidal rule with extrapolation to infinity using the terminal elimination rate constant, λ_z. Total clearance (*Cl*) was calculated by dividing the administered dose by the AUC. Mean residence time (MRT) was calculated using the area under the first moment curve (AUMC), divided by the AUC. The volume of distribution at steady state (V^{ss}) was estimated by the product of *Cl* and MRT. *Cl* and V^{ss} for the ketamine enantiomers after administration of the racemate were calculated by considering the dose of the enantiomers to be equal to 50% of the administered dose of the racemate.

Statistical analysis of data

The mean and SD, and the 95% confidence limits were used to express the central tendency of the data. Categorical variables were evaluated by chi-square analysis.

Raw data were submitted to analysis of variance (MANOVA for repeated measures—univariate—with repeated measures as "within-subject-factor" and treatment as "between-subject-factor").

The pharmacokinetic variables were analysed using two-sided Student's *t* test for paired or unpaired data, as appropriate.

t Tests were used in order to establish differences between data (haemodynamic effects, catecholamines) before and after administration of the trial medications.

In order to compare the effects of S(+)-ketamine with those of racemic ketamine, differences between data obtained after and before administration were calculated and then submitted to *t* tests for comparison.

P values < 0.05 were considered to be statistically significant. The SPSS PC+ program version 4.0 and the PC-SAS program version 6.03 were used for statistical evaluation of the data.

RESULTS

Data from four patients in the S(+)-ketamine group and one patient in the racemate group could not be included in the pharmacokinetic calculation because of unexplained fluctuations in plasma concentrations of ketamine. Because of technical problems, data from only 34 patients could be used for reliable determination of plasma catecholamine concentrations. The groups were comparable in patient characteristics (table I). All analytical assays met the acceptance criteria established before the onset of study sample analysis [18, 21]. The mean predicted concentrations of plasma quality control samples were within 3 and 11% or 5 and 17% for ketamine enantiomers or catecholamines, respectively.

The mean plasma concentration–time profiles for ketamine and norketamine enantiomers after administration of S(+)-ketamine 1 mg kg^{-1} or racemic ketamine 2 mg kg^{-1} are shown in figures 1 and 2, respectively. S(+)-Ketamine was not inverted to its optical antipode as determined by plasma analysis (fig. 1). After administration of racemate, the plasma concentration profiles of the enantiomers of ketamine and norketamine were similar (fig. 2). Pharmacokinetic variables indicated a high clearance and a moderately large volume of distribution for the ketamine enantiomers (table II), similar to data published previously [15]. The calculated parameters of S(+)-ketamine were not statistically different between treatment groups (table II). Furthermore, the pharmacokinetic variables of S(+)-ketamine following administration of the single S(+)-enantiomer were also similar to those of R(−)-ketamine after administration of the racemate (table II). However, after administration of racemate a statistically significantly smaller clearance of 13.6% (16.5 (SD 4.8) ml min^{-1} kg^{-1} compared with 19.1 (7.2) ml min^{-1} kg^{-1}; $P < 0.01$) and smaller volume of distribution at steady state of 8.6% (3.01 (1.24) litre kg^{-1} compared with 3.29 (1.29) litre kg^{-1}; $P < 0.01$) for R(−)-ketamine compared with S(+)-ketamine were found (table II).

Haemodynamic variables (systolic and diastolic arterial pressures, heart rate) increased significantly in both groups after administration of ketamine (fig. 3). There was a statistically significant difference between groups in systolic pressure at 1 min ($P < 0.003$), 3 min ($P < 0.0001$) and 15 min ($P < 0.001$) after administration of ketamine, in diastolic pressure at 1 min ($P < 0.005$), 3 min ($P < 0.0001$) and 15 min ($P < 0.001$) after administration of ketamine and in heart rate at 1 min ($P < 0.05$), 3 min ($P < 0.05$) and 10 min ($P < 0.05$) after administration of ketamine. Plasma adrenaline and noradrenaline concentrations increased and decreased similarly in both treatment groups (table III) without reaching statistical significance over the period investigated. There were no correlations between changes in haemodynamic variables and plasma concentrations

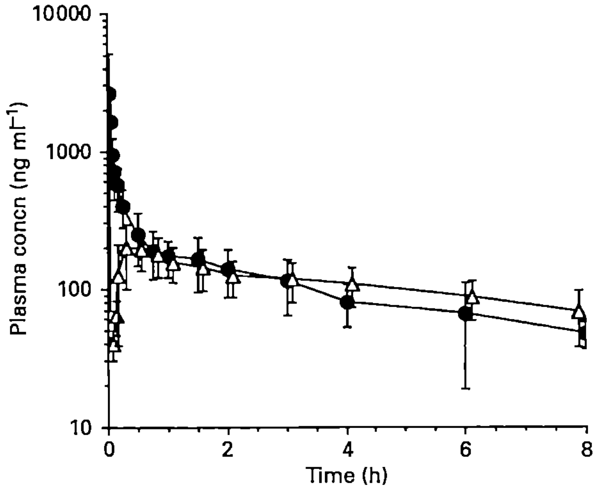


FIG. 1. Venous plasma concentrations of S(+)-ketamine (●) and S(+)-norketamine (△) (mean, SD) ($n = 21$) on a logarithmic scale as a function of time after administration of S(+)-ketamine 1 mg kg^{-1} to surgical patients.

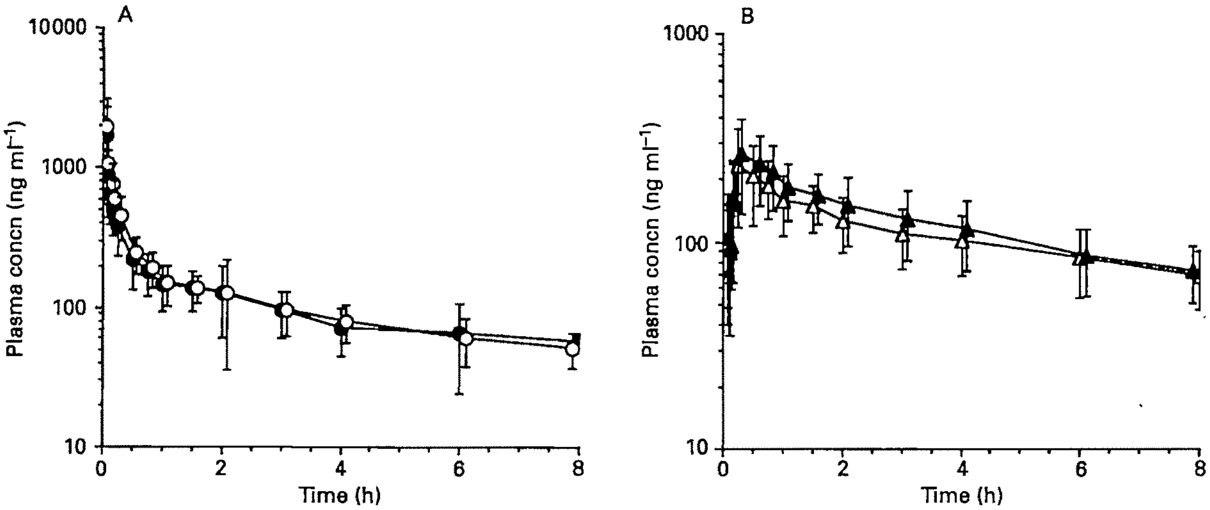


FIG. 2. Venous plasma concentrations of A: S(+)-ketamine (●) and R(−)-ketamine (○) (mean, SD) ($n = 24$) and B: S(+)-norketamine (△) and R(−)-norketamine (▲) (mean, SD) ($n = 24$) on a logarithmic scale as a function of time after administration of racemic ketamine 2 mg kg^{-1} to surgical patients.

TABLE II. *Mean (SD) [95% confidence limits] pharmacokinetic variables for the individual enantiomers of ketamine following i.v. administration of S(+)-ketamine 1 mg/kg body weight* (n = *21) and racemic drug 2 mg/kg body weight* (n = *24) to patients undergoing minor surgery. No significant difference in S(+)-ketamine variables between groups (Student's unpaired* t *test).* *P < *0.05;* **P < *0.01 for comparison of variables of S(+)- and R(−)-ketamine within group (Student's paired* t *test)*

		Racemic ketamine		
	S(+)-ketamine	S(+)-ketamine		R(−)-ketamine
AUC (µg h ml^{-1})	1119 (314)	995 (386)	*	1096 (313)
	[976–1262]	[832–1158]		[964–1228]
$T_{\frac{1}{2}}$ (h)	2.39 (1.26)	2.49 (0.79)		2.59 (0.95)
	[1.82–2.97]	[2.15–2.82]		[2.19–2.99]
MRT (h)	2.97 (1.30)	2.97 (0.85)		3.20 (1.31)
	[2.37–3.56]	[2.61–3.33]		[2.65–3.76]
Cl (ml min^{-1} kg^{-1})	16.4 (5.7)	19.1 (7.2)	**	16.5 (4.8)
	[13.8–19.0]	[16.1–22.2]		[14.5–18.5]
V^{ss} (litre kg^{-1})	2.84 (1.59)	3.29 (1.29)	**	3.01 (1.24)
	[2.12–3.56]	[2.73–3.85]		[2.47–3.54]

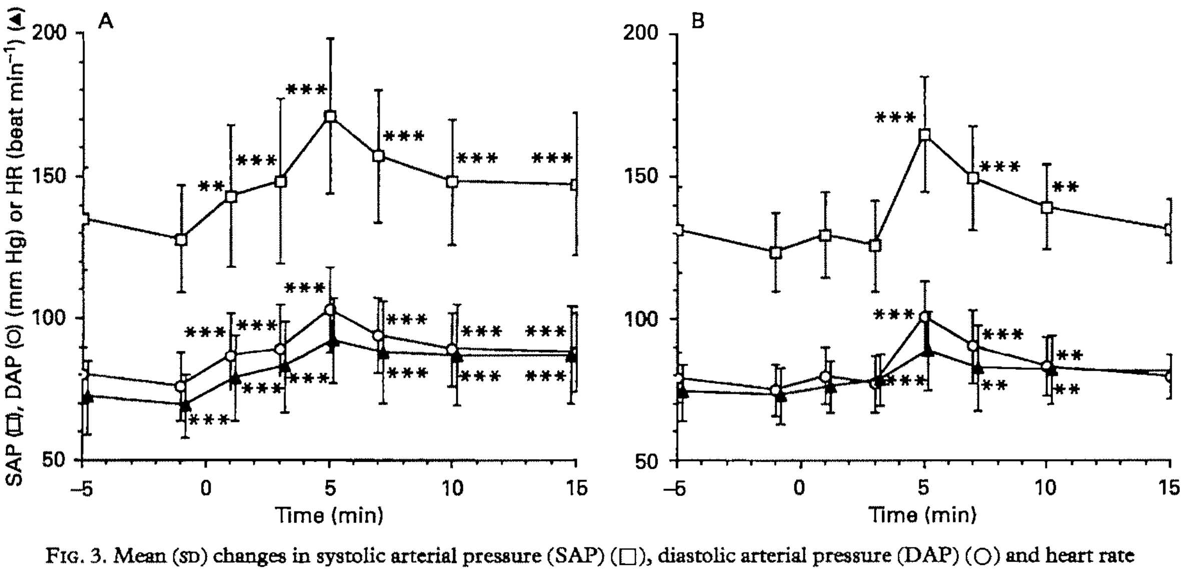


FIG. 3. Mean (SD) changes in systolic arterial pressure (SAP) (□), diastolic arterial pressure (DAP) (○) and heart rate (HR) (▲) after i.v. administration of A: S(+)-ketamine 1 mg kg^{-1} or B: racemic ketamine 2 mg kg^{-1} to surgical patients. Four minutes after ketamine administration, the patient's trachea was intubated. Baseline values of haemodynamic variables were not statistically different between the groups. **$P < 0.01$; ***$P < 0.001$ compared with baseline.

TABLE III. *Mean* (SD) *[95% confidence limits] plasma noradrenaline and adrenaline concentrations during midazolam–*S(+)*-ketamine or midazolam–racemic ketamine induction of anaesthesia in surgical patients. No statistically significant changes compared with baseline; baseline values not statistically different in both groups. Start of ketamine injection = 0 min*

	Noradrenaline (pg ml^{-1})		Adrenaline (pg ml^{-1})	
Time (min)	S(+)-ketamine ($n = 15$)	Racemate ($n = 19$)	S(+)-ketamine ($n = 15$)	Racemate ($n = 19$)
−5	259 (150) [176–341]	260 (135) [197–323]	124 (113) [58–189]	90 (75) [53–128]
−1	270 (240) [137–403]	219 (137) [155–283]	168 (258) [19–318]	129 (182) [43–215]
3	247 (198) [141–352]	210 (96) [164–256]	76 (49) [49–104]	92 (63) [61–124]
4	266 (198) [146–385]	272 (132) [199–345]	149 (257) [−13 to 313]	114 (114) [51–178]
5	350 (197) [225–475]	339 (140) [259–420]	218 (238) [58–378]	110 (79) [62–158]
7	257 (134) [176–339]	296 (129) [222–370]	93 (87) [37–149]	82 (43) [57–107]
10	377 (564) [65–690]	244 (112) [191–296]	221 (380) [2–441]	82 (68) [50–114]
15	379 (433) [140–610]	256 (100) [208–305]	170 (315) [−4 to 345]	94 (75) [56–131]

of ketamine, norketamine enantiomers or catecholamines.

DISCUSSION

It has been shown that a single dose of S(+)-ketamine 1 mg kg^{-1} produced the same EEG slowing and depth of anaesthesia as 2 mg kg^{-1} of the racemic compound [14, 15]. However, it was not known if this was a reflection of pharmacodynamic differences or stereoselective disposition. We have now examined this question using a novel, validated stereoselective assay [18].

After administration of the pure S(+)-enantiomer, no R(−)-ketamine was detected, suggesting that no inversion occurred after S(+)-ketamine. After administration of the racemic compound, the plasma concentrations of R(−)- and S(+)-ketamine of each patient were similar; therefore, inversion from R(−)- to S(+)-ketamine seems unlikely. However, this observation is not conclusive, because a possible inversion from the R(−)- form to the S(+) form could be masked by, for example, different stereoselective clearances resulting also in similar concentration profiles of both enantiomers. In fact, after administration of the racemate, we found a statistically significant ($P < 0.01$) smaller clearance of R(−)-ketamine compared with S(+)-ketamine (16.5 ml min^{-1} kg^{-1} *vs* 19.1 ml min^{-1} kg^{-1}). This finding corresponds with *in vitro* data suggesting a significantly greater metabolism of S(+)-ketamine compared with its optical antipode, whereby R(−)-ketamine inhibited the metabolism of the S(+)-enantiomer [22, 23]. These *in vitro* data, however, would also suggest greater metabolism of S(+)-ketamine after administration of pure S(+)-ketamine compared with administration of the racemate. However, this finding is not consistent with our data (table II). Possibly small differences in rates of metabolism in the presence of large interpatient variability could be the explanation. Nevertheless, the differences in stereoselective disposition after administration of racemate may be clinically relevant. The inhibition of metabolism of S(+)-ketamine by the R(−)-enantiomer as found in *in vitro* experiments [22, 23] could account for the prolongation of recovery observed after administration of racemic ketamine as speculated by White and colleagues [15]. However, based on plasma clearance calculations, we could not find evidence that R(−)-ketamine inhibited the metabolism of S(+)-ketamine (table II). Further investigations could clarify the clinical relevance of the stereoselective metabolism also in connection with a stereoselective pharmacokinetic interaction of a benzodiazepine and ketamine, described previously using racemic ketamine and non-stereoselective methods [24].

The cardiovascular changes produced by ketamine are well documented [25, 26] also for the pure enantiomers [15]. It has been reported that the hypertensive effects of ketamine may be reduced by benzodiazepines (e.g. diazepam) given 5–10 min before administration of ketamine [27]. White and colleagues [15] administered S(+)-ketamine 25 mg min^{-1}, R(−)-ketamine 75 mg min^{-1} and racemic ketamine 50 mg min^{-1} over a 5–7 min interval by constant infusion (but without midazolam premedication) and found maximal increases in mean arterial pressure and heart rate of 42–59% and 56–85%, respectively. There was no significant difference in haemodynamic variables between the three groups. In our study, the maximal increases above baseline values in systolic pressure, diastolic pressure and heart rate were 27%, 29% and 28% in the S(+)-ketamine group and 26%, 27% and 20% in the racemate group, respectively. These data suggest that the S(+)-enantiomer contributed mainly to the cardiovascular stimulation. Haemodynamic variables increased constantly in the S(+)-ketamine group, whereas in the racemate group these variables increased only 5 min after administration of ketamine (fig. 3). This might be a result of different S(+)-ketamine plasma concentration profiles immediately after administration of ketamine. The mean S(+)-ketamine plasma concentration was 2635

(2566) ng ml^{-1} 1 min after administration of pure s(+)-enantiomer, but after the racemate, the mean s(+)-ketamine concentration was only 1817 (1884) ng ml^{-1}.

It has been suggested that cardiovascular stimulation by ketamine is caused by increased sympathetic nervous system activity, with enhanced catecholamine release secondary to depression of baroreceptor reflex activity [28]. However, our study has shown, that plasma concentrations of adrenaline and noradrenaline were unaffected by either s(+)-ketamine or the racemic compound. This observation is in accordance with other studies [29, 30]. Moreover, it has been shown that the increase in plasma concentrations of catecholamines after ketamine occurred only when premedication with benzodiazepines was avoided [27, 31]. Our results support the observations of White, Way and Trevor [6] that "ketamine produces its sympathomimetic actions primarily by direct stimulation of CNS structures".

We conclude that the disposition of ketamine enantiomers after administration of racemate is stereoselective, and suggest that the use of s(+)-ketamine is more rational than use of the racemic compound.

ACKNOWLEDGEMENTS

We thank Dr B. Raffelsberger (Parke Davis, Freiburg) for the generous supply of ketamine and norketamine enantiomers and Dr K.-O. Vollmer (Parke Davis) and Dr B. Gebhardt (Parke Davis) for helpful discussions.

REFERENCES

1. Williams K, Lee E. Importance of drug enantiomers in clinical pharmacology. *Drugs* 1985; **30**: 333–354.
2. Ariens EJ. Stereochemistry: a source of problems in medicinal chemistry. *Medicinal Research Reviews* 1986; **6**: 451–466.
3. Tucker GT, Lennard MS. Enantiomer specific pharmacokinetics. *Pharmacology and Therapeutics* 1990; **45**: 309–329.
4. Drayer DE. Pharmacodynamic and pharmacokinetic differences between drug enantiomers in humans: an overview. *Clinical Pharmacology and Therapeutics* 1986; **40**: 125–133.
5. Domino EF, Chodoff P, Corssen G. Pharmacologic effects of CI-581, a new dissociative anesthetic in man. *Clinical Pharmacology and Therapeutics* 1965; **6**: 279–290.
6. White PF, Way WL, Trevor AJ. Ketamine—its pharmacology and therapeutic uses. *Anesthesiology* 1982; **56**: 119–136.
7. Corssen G, Domino EF. Dissociative anesthesia: Further pharmacologic studies and first clinical experience with a phencyclidine derivative CI-581. *Anesthesia and Analgesia* 1966; **45**: 29–40.
8. Kothary SP, Zsigmond EK. Prevention of ketamine-induced psychic sequelae by diazepam. *Clinical Pharmacology and Therapeutics* 1975; **17**: 238.
9. Marietta MP, Way WL, Castagnoli N, Trevor AJ. On the pharmacology of the ketamine enantiomorphs in the rat. *Journal of Pharmacology and Experimental Therapeutics* 1977; **202**: 157–165.
10. Ryder S, Way WL, Trevor AJ. Comparative pharmacology of the optical isomers of ketamine in mice. *European Journal of Pharmacology* 1978; **49**: 15–23.
11. Meliska CJ, Greenberg AJ, Trevor AJ. The effects of ketamine enantiomers on schedule-controlled behavior in the rat. *Journal of Pharmacology and Experimental Therapeutics* 1980; **212**: 198–202.
12. Garfield JM, Rocco J, Naulty JS. Differential effects of ketamine stereoisomers on maze performance in the mouse. *Anesthesiology* 1985; **63**: 681–683.
13. Zeilhofer HU, Swandulla D, Geisslinger G, Brune K. Differential effects of ketamine enantiomers on NMDA receptor currents in cultured neurons. *European Journal of Pharmacology* 1992; **213**: 155–158.
14. White PF, Ham J, Way WL, Trevor AJ. Pharmacology of ketamine isomers in surgical patients. *Anesthesiology* 1980; **52**: 231–239.
15. White PF, Schuettler J, Shafer A, Stanski DR, Horai Y, Trevor AJ. Comparative pharmacology of the ketamine isomers. *British Journal of Anaesthesia* 1985; **57**: 197–203.
16. Schuettler J, Stanski DR, White PF, Trevor AJ, Horai Y, Verotta D, Sheiner LB. Pharmacodynamic modeling of the EEG effects of ketamine and its enantiomers in man. *Journal of Pharmacokinetics and Biopharmaceutics* 1987; **15**: 241–253.
17. Watson E. Liquid chromatography with electrochemical detection for plasma norepinephrine and epinephrine. *Life Sciences* 1981; **28**: 493–497.
18. Geisslinger G, Menzel-Soglowek S, Kamp HD, Brune K. Stereoselective high-performance liquid chromatographic determination of the enantiomers of ketamine and norketamine in plasma. *Journal of Chromatography* 1991; **568**: 165–176.
19. Gibaldi M, Perrier D. *Pharmacokinetics*, 2nd Edn. New York: Marcel Dekker, Inc., 1982.
20. Heinzel G. Topfit. In: Bozler G, van Rossum JM, eds. *Pharmacokinetics During Drug Development: Data Analysis and Evaluation Techniques*. Stuttgart: Fischer Verlag, 1982: 207–208.
21. Shah VP, Midha KK, Dighe S, McGilveray IJ, Skelly JP, Yacobi A, Layloff T, Viswanathan CT, Cook CE, McDowall RD, Pittman KA, Spector S. Analytical methods validation: bioavailability, bioequivalence and pharmacokinetic studies. *International Journal of Pharmaceutics* 1992; **82**: 1–7.
22. Trevor AJ, Woolf TF, Baillie TA, Adams JD, Castagnoli N. Stereoselective metabolism of ketamine enantiomers. In: Kamenka JM, Domino EF, eds. *Phencyclidine and Related Arylcyclohexylamines: Present and Future Applications*. Ann Arbor: NPP Books, 1983; 279–289.
23. Kharasch ED, Kunze K, Herrmann S. Stereochemical aspects of human liver microsomal ketamine metabolism. *Anesthesiology* 1991; **75**: A382.
24. Domino EF, Domino SE, Smith RE, Domino LE, Goulet JR, Domino KE, Zsigmond EK. Ketamine kinetics in unmedicated and diazepam-premedicated subjects. *Clinical Pharmacology and Therapeutics* 1984; **36**: 645–653.
25. Tweed WA, Minuck MS, Mymin D. Circulatory responses to ketamine anesthesia. *Anesthesiology* 1972; **37**: 613–619.
26. Idvall J, Ahlgren I, Aronsen KF, Stenberg P. Ketamine infusions: pharmacokinetics and clinical effects. *British Journal of Anaesthesia* 1979; **51**: 1167–1173.
27. Zsigmond EK, Domino EF. Clinical pharmacology of ketamine. In: Domino EF, ed. *Status of Ketamine in Anesthesiology*. Ann Arbor: NPP Books, 1990; 27–76.
28. Dowdy EG, Kaya K. Studies of the mechanism of cardiovascular responses to CI-581. *Anesthesiology* 1968; **29**: 931–943.
29. Tokics L, Brismar B, Hedenstierna G, Lundh R. Oxygen uptake and central circulation during ketamine anaesthesia. *Acta Anaesthesiologica Scandinavica* 1983; **27**: 318–322.
30. Kreuscher HP, Braune JP, Lechner MD. Computer supported infusion profiles for long lasting anesthesia with ketamine-midazolam. In: Domino EF, ed. *Status of Ketamine in Anesthesiology*. Ann Arbor: NPP Books, 1990; 305–318.
31. Zsigmond EK, Kothary SP, Matsuki A, Kelsch RC. Diazepam for prevention of the rise in plasma catecholamines caused by ketamine. *Clinical Pharmacology and Therapeutics* 1974; **15**: 223–224.

British Journal of Anaesthesia 1993; **70**: 672–680

REVIEW ARTICLE

PREVENTION AND TREATMENT OF HYPOTENSION DURING CENTRAL NEURAL BLOCK

A. F. McCRAE AND J. A. W. WILDSMITH

The management of hypotension occurring during central neural block is a subject of some contention, with proponents for the use of either volume loading or vasopressors expressing dogmatic views. It is important not to be too specific in the approach to this problem and to treat each patient on individual merit, recognizing that many factors may influence arterial pressure during anaesthesia and surgery.

CONTROL OF ARTERIAL PRESSURE

Arterial pressure is the product of cardiac output and systemic vascular resistance and both of these variables are influenced by many factors (fig. 1). Cardiac output is determined by venous return according to the Frank Starling law. Venous return is influenced by gravity, the calf muscle pump, intrathoracic pressure and the degree of venomotor tone, which is matched to circulating blood volume. Systemic vascular resistance is determined by sympathetic vasomotor tone and by the influence of hormones such as renin, angiotensin, aldosterone and antidiuretic hormone. Endogenous vasopressin (antidiuretic hormone) also contributes to maintenance of arterial pressure during extradural anaesthesia [51]. The vasomotor centre in the brain stem controls the degree of sympathetic tone in a feedback loop involving the baroreceptors. Other factors affecting arterial pressure such as pain, exercise and emotion act directly through the vasomotor centre, which also receives input from the chemoreceptors.

Changes within the microcirculation may also influence arterial pressure, although it is more usual to think of those factors as being responsible for autoregulation of flow. There are two main mechanisms: myogenic and chemical. Myogenic autoregulation acts via stretch receptors in vessel walls which cause them to constrict when pressure is decreased. Chemical autoregulation is mediated by the local concentration of vasoactive metabolites. In the presence of vasodilatation, as produced by sympathetic block, an increase in flow washes out the metabolites and produces reflex vasoconstriction.

ORGAN PERFUSION

Although it is arterial pressure that we measure and adjust, it is important to remember that organ flow is the vital factor. Compensatory mechanisms ensure that flow to vital organs is maintained over a wide range of pressures.

Coronary blood flow is autoregulated between 60 and 150 mm Hg. If coronary perfusion pressure decreases, the myocardium becomes relatively hypoxic and ADP accumulates. This is converted to adenosine, a potent coronary vasodilator, which restores local blood flow. A decrease in arterial pressure results in decreased left ventricular work and oxygen demand. Therefore hypotension may have a benign effect unless there is concomitant tachycardia or a significant pressure gradient across the aortic valve, both of which impair coronary artery filling during diastole.

Cerebral blood vessels are devoid of sympathetic nerve supply and autoregulation of flow occurs between 50 and 180 mm Hg by reflex arteriolar constriction in hypertension or vasodilatation in hypotension. Thus normal cerebral blood flow is maintained until mean arterial pressure is less than 50 mm Hg. At such a pressure, ischaemia occurs, leading to local hypercapnia and hypoxia, both of which stimulate the vasomotor centre chemically to increase sympathetic tone and systemic vascular resistance in an attempt to restore arterial pressure.

Renal autoregulation occurs between 80 and 180 mm Hg. The afferent glomerular arteriole has a myogenic response to stretch and constricts with hypertension and dilates with hypotension to maintain a constant renal perfusion pressure. This can be overriden by the sympathetic innervation of the kidney. A small decrease in arterial pressure produces sympathetic stimulation and causes vasoconstriction of the efferent arteriole to maintain filtration pressure in the glomerulus in the presence of decreased renal blood flow. A more marked decrease in arterial pressure and more intense sympathetic stimulation results in constriction of the afferent

(Br. J. Anaesth. 1993; **70**: 672–680)

KEY WORDS

Anaesthetic techniques: extradural, spinal. Arterial pressure: hypotension. Complications: hypotension.

A. F. McCRAE, D.R.C.O.G., F.F.A.R.C.S.I.; J. A. W. WILDSMITH, M.D., F.R.C.ANAES.; Department of Anaesthetics, Royal Infirmary, Lauriston Place, Edinburgh EH3 9YW.

Correspondence to A. F. McC.

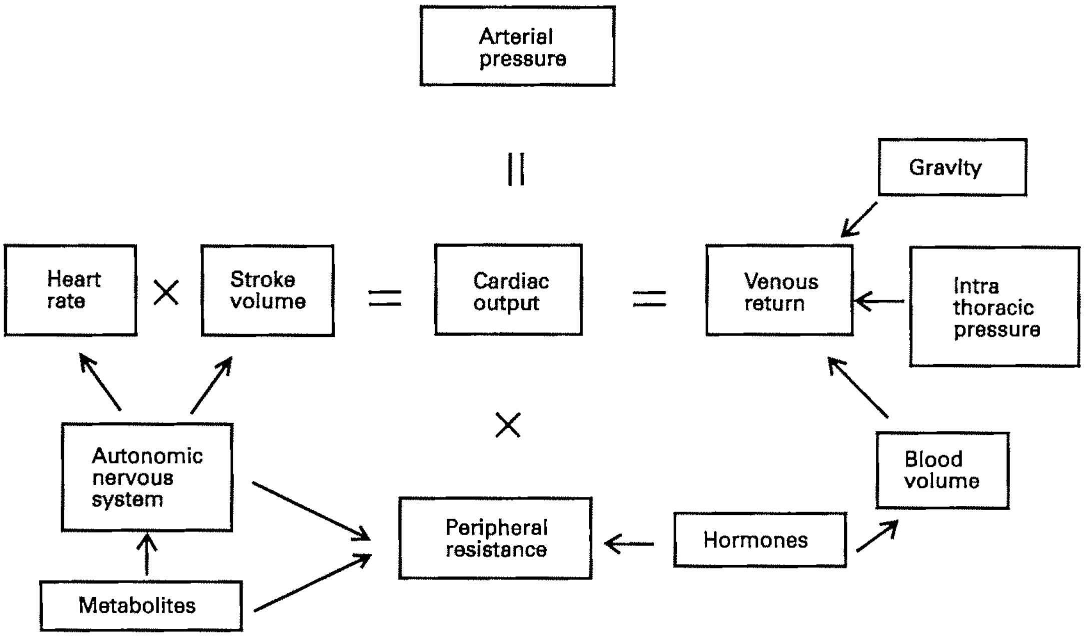


FIG. 1. Major factors influencing arterial pressure during central nerve block.

arteriole and a decrease in both renal blood flow and glomerular filtration. In clinical practice, glomerular filtration rate is reduced only to a small extent (10 %) during central neural block and this is not enough to cause significant impairment of normal renal function [30].

CIRCULATORY EFFECTS OF CENTRAL BLOCK

Hypotension during central neural block is mainly a result of decrease in systemic vascular resistance which occurs by block of preganglionic sympathetic fibres. This allows vasodilatation and an increase in venous capacitance with venous pooling, unless gravity is used to maintain venous return. Hypotension is more likely to occur in dehydrated or hypovolaemic patients.

The major factor in the development of hypotension is the level of block. The sympathetic outflow is between T1 and L2, so that a block below that level has no effect on arterial pressure, but one to T8 "sympathectomizes" the lower half of the body. The sympathetic supply to the adrenal medulla is from T8 to L1 and central neural block alters arterial pressure by inhibition of the systemic release of catecholamines. Fibres from T2 to T4 provide the sympathetic supply to the heart, and decreased contractility and bradycardia (from unopposed vagal activity) ensues if they are blocked. *Although vagal overactivity may cause severe hypotension in individual patients,* changes in arterial pressure relate more usually to the level of block than to vagal efferent activity as measured by ECG R–R intervals [13]. A block as high as T1 totally removes the ability of the body to compensate for other circulatory changes in addition to producing extensive vasodilatation.

The level of sympathetic block is in general higher than the sensory block, but the situation is complex. The differential cephalad extent of block has been reported as two segments if loss of temperature discrimination is used as the measurement of sympathetic block [23] and six segments if thermographic imagery techniques are used to measure small changes in skin temperature [6]. Sympathetic block may also be incomplete. Only 60 % of patients undergoing spinal anaesthesia had complete sympathetic block as demonstrated by skin conductance response measurements [41]. Such measurements correlate with changes in conductance resulting from sweating with sympathetic nervous system activity, although other workers have cast doubt on the use of this method as a measure of the completeness of sympathetic block [31]. The duration of sympathetic block may not be as long as previously thought, and one study has shown that motor and sensory block outlast it [3]. However, this may simply indicate that hormonal and capillary reflexes compensate for the sympathetic block and obscure its effects.

Type of central block

There are differences between spinal and extradural block. The degree of sympathetic block tends to be greater, and the onset of hypotension tends to be faster, after spinal than after extradural injection, because the speed of onset of the block is faster than the development of physiological compensation [14]. Individual variations in technique such as speed of injection, the use of barbotage in spinal or an incremental technique in extradural block [15] may cause different degrees of hypotension by altering the height of block obtained and the rate at which it develops.

Alterations to the local anaesthetic solutions, such as changing the baricity of the agent used in spinal anaesthesia to manipulate the height of block, may influence the development of hypotension [1]. Adding adrenaline tends to produce a more profound central block and therefore greater decreases in mean arterial pressure and systemic vascular resistance, but the changes may be modified further by the direct effect of adrenaline on peripheral resistance, heart rate and cardiac output. The use of alkalinized

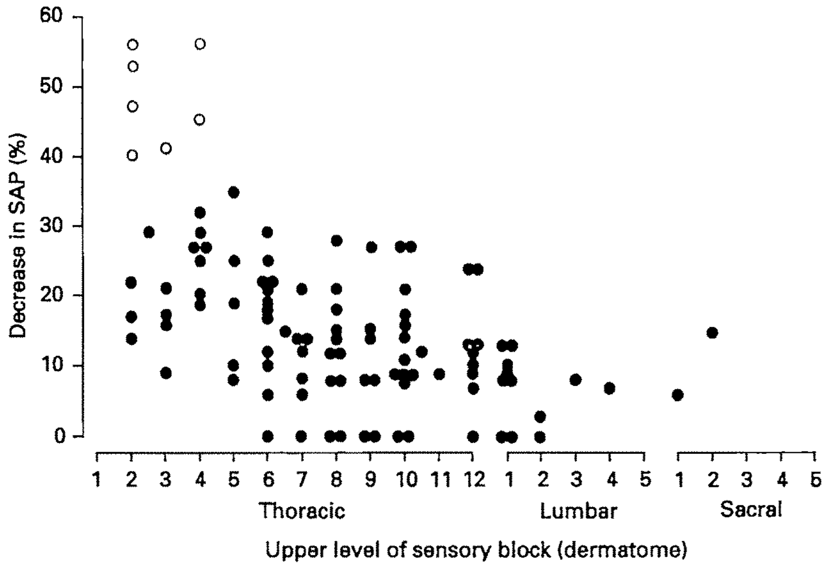


FIG. 2. Relationship between upper level of sensory block and per cent decrease in systolic arterial pressure (SAP) in 100 patients given amethocaine in a variety of solutions. No prophylactic treatment was given. O = Seven patients who required treatment with atropine or ephedrine because of clinical circulatory inadequacy. (Reproduced with permission [38].)

lignocaine in extradural block is associated with both a greater degree and more rapid onset of hypotension than non-alkalinized solutions [50]. Finally, the systemic effect of a large dose of local anaesthetic is myocardial depression and this may also influence the arterial pressure.

THE OBSTETRIC PATIENT

The obstetric patient presents additional problems. In the supine position, the inferior vena cava may be occluded completely by the pregnant uterus. Unless adequate venous return occurs through the collateral system of extradural and azygous veins, decreased arterial pressure and uterine blood flow result [35]. The aorta may also be compressed and, although this may not produce symptoms in the mother, uterine blood flow decreases, resulting in fetal distress and neonatal depression. This syndrome of supine hypotension by aortocaval compression may occur from 20 weeks onwards [8] and is relieved by the mother adopting the left lateral position. Although delivery of the baby also relieves the situation, it may be associated with an acute loss of circulating volume and compensation may be impaired seriously if the block is extensive.

TREATMENT

Defining hypotension

A variety of options is available for both prevention and treatment of hypotension caused by central block. These have been researched extensively, but there are many problems in comparing studies in this field. Although the variability of "resting" arterial pressure is widely recognized, it is unusual for the status of the control figure to be defined clearly. Second, arbitrary definitions of hypotension have been chosen by different authors: systolic arterial pressure < 100 mm Hg or < 90 mm Hg, 20 % or 30 % decreases from baseline or any 30-mm Hg decrease in systolic pressure have been used. In some studies, changes in mean rather than systolic arterial pressure were analysed and relatively few studies have been fully randomized. Frequently, only patients who became hypotensive were studied!

Such factors have favoured the preconceived notion that all patients become hypotensive during central nerve block and as a result there are few studies with true control groups in which no intervention was used. Figure 2 [38] relates the percent change in systolic pressure to the level of block in 100 non-obstetric patients who received a variety of regional techniques, but no prophylaxis for hypotension other than a 5° head-down tilt. The risk of hypotension increased with height of block, but many patients with extensive blocks had minimal changes in arterial pressure.

General points

Because a high level of block is a major determinant of the development of hypotension, choosing a block limited to suit the planned procedure prevents unnecessary decreases in arterial pressure. Haemorrhoidectomy does not require a block higher than S1, whereas abdominal hysterectomy needs a block of T10 at least. In any patient receiving a central nerve block, venous return should be maintained by a slight (5–10°) head-down tilt to eliminate venous pooling in the legs, and by the use of left-lateral tilt in obstetric patients.

Infusions and combined blocks have been advocated as being less likely to produce significant hypotension. When continuous extradural infusions are used in labour, the majority of episodes of hypotension occur in relation to the initial loading dose [20]. If a bolus of the dilute solution intended for the infusion is used as a loading dose rather than a more concentrated local anaesthetic, the incidence of hypotension is reduced from 35% to 7%, although there is some increase in onset time [40].

The combined spinal-through-extradural needle technique decreases the incidence of hypotension by producing rapid establishment of a spinal block of the lower segments followed by careful extension of the block using bolus extradural injections. During Caesarean section using the combined technique, the incidence of hypotension was 33% compared with 53% in a conventional extradural group. Another advantage was a reduction in the total dose of local anaesthetic to approximately 33% of that used in the conventional group [56].

The use of combined spinal-through-extradural needle techniques have *not* produced problems of accidental high block with associated severe hypotension [11, 18, 33]. However, spinal block performed *after* extradural anaesthesia may result in a very extensive block and severe hypotension [2, 64]. Possibly, local anaesthetic passes through the puncture wound in the dura or, more likely, the subarachnoid space is compressed by the large volume of local anaesthetic present in the extradural space [2].

Hypotension during spinal anaesthesia may be reduced using a catheter technique. A retrospective study of elderly patients undergoing orthopaedic surgery found that hypotension occurred less frequently, and fewer doses of vasopressor were required during continuous spinal anaesthesia than during continuous extradural block [65].

Mechanical methods

Several mechanical methods of compressing the lower limbs, in order to encourage venous return, have been used with varying degrees of success. In studies of Caesarean section under spinal anaesthesia, the application of Esmarch bandages from ankle to mid-thigh decreased the incidence of hypotension from 83% to 16% [4], and inflatable full length leg splints (normally used for fracture stabilization) from 83% to 48% [22], but inflatable boots produced no significant effect [27]. However, a different volume of fluid was given in each of these studies: 20 ml kg^{-1} in the first, 15 ml kg^{-1} in the second and 10 ml kg^{-1} in the third. During extradural Caesarean section, elastic bandages were found to reduce the incidence of hypotension from 83% to 13% [21], but graduated compression stockings made no significant difference, the incidence of hypotension being 30% in both groups [34]. However, the volumes of fluid administered were different; Ringer's lactate solution 15 ml kg^{-1} in the first study and only 500 ml in the second. It would appear that none of these methods is entirely reliable in preventing hypotension.

Additional mechanical methods have been used in obstetric patients to eliminate supine hypotension, by displacing the uterus, either by a special device or by adopting the full left-lateral position. In pregnant women at term, a comparison between the supine or left-lateral "wedged" positions with either the Colon–Morale or Kennedy uterine displacement device found that the wedge was more effective than mechanical displacement of the uterus [19]. One interesting study looked at the inter-relationship between fluid loading and mechanical displacement in patients undergoing Caesarean section with a spinal anaesthetic. In elective patients, the incidence of hypotension was 92% in an untreated control group, 57% after 1000 ml of crystalloid and 53% with mechanical displacement and crystalloid [10]; in a group of emergency Caesarean sections, the incidences were 50%, 46% and 15%. The lesser frequency of hypotension in the labouring groups was perhaps the result of contractions autotransfusing blood from the uterine vessels to the general circulation. It seems that mechanical devices have little to offer, as they merely displace the centre of gravity, whereas tilt alters the direction of force.

Volume loading

The effect of i.v. fluid loading is to increase stroke volume and cardiac output [58], although these return to control values after institution of a central block. Both crystalloid and colloid have been used to compensate for these changes and arguments have been advanced for the use of each. In general, the use of crystalloid requires a larger volume than colloid and this might be expected to cause pulmonary oedema in an at-risk patient, but one study found this not to be the case [68]. Colloid may stay in the intravascular compartment longer, but is more expensive and some of the solutions confer a small, but significant, risk of anaphylaxis [63].

Large volumes of fluid may not be desirable in some circumstances, and may be frankly dangerous in elderly patients with poor cardiac function, in whom there is a risk of pulmonary oedema and cardiac failure. Routine volume loading may be unnecessary in these patients unless they are dehydrated. Ringer's acetate solution 0, 8 or 16 ml kg^{-1} was given to elderly patients having lower limb or lower abdominal operations under spinal anaesthesia, but the incidence of hypotension (24–32%) was not significantly different between the groups [12]. Obstetric patients are also at increased risk of pulmonary oedema, because interstitial lung water is increased during the puerperium [39]. A possible further complication of large volume administration is the development of urinary retention. Sympathetic vascular tone returns before bladder sensation as a block regresses, so that overdistension occurs while the patient is unaware [7].

In a small study of spinal anaesthesia for Caesarean section or vaginal delivery, pretreatment with 1000 ml of 5% glucose in Ringer's lactate solution prevented any significant decrease in arterial pressure from baseline, whereas the control group all became hypotensive (to a greater extent in the patients with a higher block for Caesarean section) [71]. A larger preload (2000 ml) of Ringer's lactate solution was used in an open study of Caesarean section under extradural block and only 6.7% of patients had a decrease in arterial pressure greater than 20% from baseline [36]. Therefore volume loading was concluded to be a satisfactory method of preventing hypotension. In contrast, a recent study of Caesarean section under spinal anaesthesia compared volume loading with crystalloid 20 ml kg^{-1} given over 20 or 10 min. The incidence of hypotension was still 60 % and 70 %, respectively, and three of 10 patients in the latter group had unacceptable increases in central venous pressure [60].

It has been argued that colloid produces a more sustained and more effective expansion of the intravascular space and several studies have compared colloid with crystalloid in the prevention of hypotension during central neural block.

In extradural Caesarean section, a regimen of Ringer's lactate 500 ml + gelatin 500 ml solutions proved superior to 1000 ml of Ringer's lactate solution and reduced the incidence of hypotension from 45 % to 10 % [25]. Similarly, Dextran 70 solution 7.5 ml kg^{-1} was more effective than Ringer's lactate solution 15 ml kg^{-1}, reducing the incidence of hypotension from 25 % to 5 % [70]. Using thoracic electrical bioimpedance, the latter study also demonstrated a smaller thoracic fluid index, indicating less lung water in the patients given colloid. In patients having lower limb operations under extradural block, volume loading with 500 ml of low and medium molecular weight hetastarch, Dextran 70 and balanced salt solution were compared [32]. The requirement for etilefrine (ethyl-norphenylephrine) to maintain arterial pressure was not significantly different between the groups, although there was a trend towards greatest usage in the balanced salt solution group, less in the hetastarch groups and least in the Dextran group.

However, other studies of extradural Caesarean section have shown no benefit of colloid compared with crystalloid. One compared Ringer's lactate solution 1200 ml, with similar volumes of Ringer's lactate solution combined with albumin and found no significant difference in mean arterial pressure or ephedrine requirement [55]. Another study compared Ringer's lactate solution 2000 ml with Hetastarch solution 1000 ml and also found no difference between the groups [45]. During Caesarean section under spinal anaesthesia, Ringer's lactate solution 15 ml kg^{-1} with 5 % glucose was compared with the same solution containing 5 % albumin; 50 % of the patients in each group were then given ephedrine 25 mg by i.m. injection. No patient given albumin developed significant hypotension, whereas hypotension occurred in approximately 30 % of the crystalloid groups, with or without ephedrine [42].

Taken overall, these studies are contradictory, even in the incidence of hypotension in the "control" groups. Infusion of large volumes of fluid has been shown to overload the right side of the heart [46] and requires that all patients are "treated" before the spinal or extradural needle is sited. This may result in a significant proportion of patients who would not have become hypotensive receiving a large fluid load. Perhaps a more physiological approach to the treatment of hypotension induced by sympathetic block is to counteract it as it occurs, by using sympathomimetic drugs.

Vasopressors

A large proportion of the studies which have been performed have involved obstetric patients. However, there has been concern over the use of vasopressors in obstetric practice, particularly methoxamine, which may decrease uteroplacental blood flow [53]. A possible added complication is the development of severe hypertension if prophylactic vasopressors are used in conjunction with oxytocic drugs [5], particularly in a mother with pre-eclampsia or essential hypertension. This is less likely since synthetic oxytocin replaced the pituitary derivative "Pitocin" which may have been contaminated with vasopressin.

Without volume loading or lateral tilt, the incidence of hypotension in Caesarean section under central neural block exceeds 90 % [10] and most studies of vasopressors in obstetric patients include preliminary volume loading of the patient. This makes evaluation of the effect of vasopressors difficult.

Ephedrine is the most commonly used vasopressor. It has direct and indirect mechanisms of action and stimulates both alpha and beta receptors to increase cardiac output, heart rate, systolic and diastolic arterial pressure. Coronary, cerebral and muscle blood flow are increased, while renal and splanchnic blood flow are decreased [69]. Ephedrine was used first in 1927 to counteract hypotension caused by spinal anaesthesia [47], and early administration to prevent a decrease in arterial pressure was advocated, rather than treating hypotension after it had developed. In a double-blind study during Caesarean section under spinal anaesthesia, patients were given crystalloid 1000 ml and an i.m. injection of ephedrine 50 mg or placebo before the block [24]. All patients in the placebo group became hypotensive (*in spite of the volume load*), compared with only 25 % in the ephedrine-treated group. An increase in systolic arterial pressure occurred in all the ephedrine-treated patients, but significant hypertension did not develop.

A larger, randomized study of prophylactic i.m. ephedrine in extradural Caesarean section compared placebo and i.m. ephedrine 25 mg or 50 mg after volume loading with 1000 ml of crystalloid. The incidence of hypotension was less in this study (8–12 %) and was similar in all the groups. Persistent hypertension was observed in 66 % of the group given ephedrine 50 mg and the study was discontinued for this reason [59].

In non-obstetric patients, development of hypotension is related to the general physical condition of the patient. Patients in ASA grades I–III undergoing spinal anaesthesia for lower body surgery and preloaded with isotonic saline–glucose solution 7 ml kg^{-1} received either placebo or ephedrine 12.5 mg i.v. + 37.5 mg i.m. [26]. No patient given ephedrine became hypotensive, but in the control groups hypotension occurred in 0 %, 12.5 % and 50 % of patients graded ASA, I, II and III, respectively.

I.m. injections of ephedrine before central neural block have unpredictable absorption and peak effect, and do not reliably prevent hypotension. In addition, large bolus doses may cause unacceptable hypertension, so it may be preferable to await the onset of hypotension and then to administer treatment. In a non-random study during Caesarean section with spinal anaesthesia, patients were given crystalloid 1500 ml and allocated to three groups after the block. The control group were those in whom no decrease in arterial pressure occurred (37 %). The remainder were treated with either bolus doses of ephedrine when systolic pressure decreased to less than 100 mm Hg, or as soon as any decrease in arterial pressure from baseline was observed. Episodes of nausea and vomiting caused by hypotension were significantly less frequent in the patients treated early [17].

Vasopressor therapy may be adjusted to the degree of hypotension using an infusion. In a study during Caesarean section with spinal anaesthesia, patients received volume loading with Ringer's lactate solution 15 ml kg^{-1} and were treated with either ephedrine 20 mg i.v. followed by 10-mg doses if arterial pressure decreased to 80 % of baseline, or with ephedrine 10 mg i.v. followed by an infusion of ephedrine adjusted to maintain systolic pressure at 90–105 % of baseline [29]. Total ephedrine dosage was similar in the two groups, but nausea was more frequent in the bolus group (36 %) than in the infusion group (5 %).

Etilefrine (ethyl-norphenylephrine), used in central Europe and Scandanavia, was compared with ephedrine in a randomized study in elderly patients undergoing hip surgery with spinal anaesthesia. Preliminary fluid administration was small, and all patients whose mean arterial pressure decreased by at least 25 % were included in the study. Hypotension was treated with repeated i.v. bolus doses of vasopressor. Both were equally effective in restoring systolic pressure, but ephedrine was more effective in restoring mean and diastolic arterial pressures [66].

Methoxamine acts on alpha receptors to cause peripheral vasoconstriction, with reflex slowing of heart rate [69]. In a retrospective study of Caesarean section under spinal anaesthesia with non-standardized volume loading and no lateral positioning, patients were given prophylactic ephedrine 50 mg, methoxamine 10–12 mg or no vasopressor [44]. Hypotension still occurred in a significant percentage of the patients in both treated groups, and postpartum hypertension in 8 % of the methoxamine group, compared with only 0.8 % in the ephedrine group. A subsequent study showed that methoxamine was associated with a significant risk of decreased uterine perfusion and its use is no longer advocated in obstetric patients [53], although it may have a role in the extreme situation of severe hypotension unresponsive to other methods, especially if the patient has tachycardia.

Phenylephrine has alpha effects identical to those of methoxamine, but also has some weak beta effects and is normally given by infusion [69]. Bolus i.v. administration of phenylephrine 100 µg has been compared with ephedrine 5 mg in the prevention of hypotension during extradural block for Caesarean section after a preload with Ringer's lactate solution 1200 ml [54]. Both drugs were equally effective. Care is required if phenylephrine is given after ephedrine, or in doses greater than 100 µg per bolus. Two cases of overdose resulting in extreme hypertension and headache have been reported, and a recommendation made that no more than 20–40 µg should be given [67].

Dihydroergotamine is a partial alpha agonist which constricts capacitance vessels only and increases systemic vascular resistance in areas subjected to sympathetic block [52]. (In greater doses it also caused prolonged and forceful uterine contraction.) In a study of non-pregnant patients undergoing extradural anaesthesia, volume loading was with crystalloid 2000–3000 ml, and patients were randomized to receive either placebo or dihydroergotamine 0.5 mg by i.v. injection [43]. There was no difference in systolic arterial pressure between the groups and the authors comment that a larger dose might have been more effective.

Mephentermine has direct and indirect sympathomimetic actions which increase cardiac contraction and venous tone and hence increase arterial pressure. It has a prolonged action (4 h) after i.m. injection [69]. Mephentermine has been studied in patients having transurethral prostatectomy under spinal anaesthesia using a variety of local anaesthetic agents and doses [16]. There were four groups of patients who received a preload of 5 % glucose 500 ml, mephentermine 30 mg i.m., a combination of both, or no treatment. Hypotension occurred in 44 % of both the control and the volume loaded groups, but was significantly reduced, to 24 % by mephentermine and to 4 % with combined therapy.

Metaraminol has direct and indirect alpha effects which produce vasoconstriction which may affect peripheral vessels selectively, thus increasing systolic and diastolic pressures and producing a reflex bradycardia [69]. *Dobutamine* has pure $beta_1$ sympathomimetic effects, increasing the force of myocardial contraction [69]. Metaraminol and dobutamine infusions have been compared in patients having major abdominal surgery under extradural anaesthesia [28]. Both agents increased systemic and pulmonary pressures and cardiac work and appeared to be equally effective in preventing hypotension. Dobutamine was preferred because of its selective action on the heart and lack of effect on total peripheral resistance.

Dopamine, the precursor of noradrenaline, causes vasoconstriction through alpha receptor stimulation when used in large doses [69], and it may be an ideal agent to use in the prevention of hypotension because of its rapid onset and short duration of action. In a study during Caesarean section under spinal anaesthesia, 78 % of the patients became hypotensive and were allocated randomly to receive an infusion of dopamine 2–10 µg kg^{-1} min^{-1} or i.v. boluses of ephedrine 10 mg [9]. The remaining 22 % of patients who did not show any decrease in arterial pressure formed the control group. Although dopamine proved effective, it was no more so than intermittent ephedrine. Dopamine 4 µg kg^{-1} min^{-1} has been shown to increase mean arterial pressure, cardiac output and heart rate during thoracic extradural anaesthesia in which volume loading with 5 % albumin 500 ml with crystalloid 1000 ml was not effective in preventing hypotension [37].

Adrenaline is a potent alpha and beta stimulator. Its predominant effect is to increase systolic pressure by direct myocardial stimulation, increased heart rate and vasoconstriction in the skin, mucosa and kidneys [69]. In a study in anaesthetized, splenectomized sheep, extradural analgesia was performed and decreases in arterial pressure and peripheral resistance were observed. Administration of Dextran 70, 10 mg kg^{-1} produced a small increase in arterial pressure secondary to increased stroke volume, but this was counteracted by a further decrease in total peripheral resistance. Administration of adrenaline approximately 1 $\mu g\ kg^{-1}\ min^{-1}$ reversed the hypotension by increasing cardiac output secondary to improved contractility and venous return. There was no effect on peripheral resistance [49]. This study showed that plasma expansion alone was insufficient to counteract systemic hypotension, but that adrenaline can restore arterial pressure without adverse effects on regional perfusion. In elderly patients undergoing total hip replacement with hypotensive extradural anaesthesia, low dose adrenaline infusion was used effectively to maintain arterial pressure at 50–55 mm Hg, by increasing cardiac index and stroke volume without change in heart rate [61].

Prenalterol, a $beta_1$ receptor agonist has been used in a small study of thoracic extradurals for aortic aneurysm surgery. Hypotension occurred in all patients and was treated with prenalterol 10 mg by i.v. infusion. Arterial pressure was rapidly restored as a result of increased cardiac output without any increase in heart rate or vascular resistance [57].

SUMMARY

Hypotension during central neural block may occur by three main mechanisms: decrease in venous return (in turn influenced by posture, bleeding and inferior vena cava compression), vasodilatation and decreased cardiac output. It is also important to recognize that, occasionally, other factors play a part. Bladder distension during central nerve block has been shown to produce hypotension inappropriate to the level of block [48, 62] and vagal overactivity may contribute in the unsedated patient. Preventive measures to reduce the likelihood of hypotension include correction of hypovolaemia, restriction of the upper level of block, use of a slight head-down tilt to maintain venous return and judicious use of sedation, especially in anxious patients. In the obstetric patient, the single most important factor in eliminating hypotension is the use of full left-lateral tilt. Mechanical methods to improve venous return by compressing the legs are not particularly helpful. Volume loading does not guarantee maintenance of arterial pressure and excessive fluid may be harmful in patients with bladder neck obstruction or at risk of pulmonary oedema. The administration of up to 1 litre before surgery may be particularly advisable if significant blood loss is expected (no matter what the anaesthetic technique), but colloid solutions do not have clear proven benefit over crystalloid.

The prevention or treatment of hypotension induced by central block by administration of large volumes of fluid is a more contentious subject, although the practice is widespread. Review of the literature has shown that many studies have been poorly designed and the results have often been contradictory, even in such basic principles as the incidence of hypotension in control groups. There is a need for evidence based on correctly designed studies comparing tightly designed treatment regimens. One such study [72] has recently shown the benefit of ephedrine compared with both volume loading and methoxamine in the prophylaxis of cardiovascular changes during combined extradural and general anaesthesia. In the treatment of hypotension, vasopressors can be much more rapidly effective and directly reverse the physiological changes produced by the block. Early intervention with small i.v. doses (e.g. ephedrine 3–6 mg or methoxamine 1–2 mg) if arterial pressure decreases towards an unacceptable value provides better control than large i.m. doses given before the block. Finer control can be achieved by using a suitable drug in an infusion. Ephedrine is probably the most useful drug in terms of safety and efficacy, but a drug with predominantly alpha agonist activity (e.g. methoxamine) may be more appropriate if heart rate is increased, especially if the response to ephedrine is poor. The decision on *what* degree of hypotension requires treatment can be made only for individual patients, but there are few who cannot tolerate a decrease of 25–30% quite safely.

REFERENCES

1. Bannister J, McClure JH, Wildsmith JAW. Effect of glucose concentration on the intrathecal spread of 0.5% bupivacaine. *British Journal of Anaesthesia* 1990; **64**: 232–234.
2. Beck GN, Griffiths AG. Failed extradural anaesthesia for Caesarean section. Complication of subsequent spinal block. *Anaesthesia* 1992; **47**: 690–692.
3. Bengtsson M, Lofstrom JB, Malmqvist LA. Skin conductance responses during spinal analgesia. *Acta Anaesthesiologica Scandinavica* 1985; **29**: 67–71.
4. Bhagwanjee S, Rocke DA, Rout CC, Koovarjee RV, Brijball R. Prevention of hypotension following spinal anaesthesia for elective Caesarean section by wrapping of the legs. *British Journal of Anaesthesia* 1990; **65**: 819–822.
5. Cassady GN, Moore DC, Bridenbaugh LD. Postpartum hypertension after the use of vasoconstrictor and oxytocic drugs. *Journal of the American Medical Association* 1960; **172**: 1011–1015.
6. Chamberlain DP, Chamberlain BDL. Changes in the skin temperature of the trunk and their relationship to sympathetic blockade during spinal anesthesia. *Anesthesiology* 1986; **65**: 139–143.
7. Charlton JE. The management of regional anaesthesia. In: Wildsmith JAW, Armitage EN, eds. *Principles and Practice of Regional Anaesthesia*. Edinburgh: Churchill Livingstone, 1987; 52–54.
8. Cheek TG, Gutsche BB. Maternal physiologic alterations during pregnancy. In: Shnider SM, Levinson G, eds. *Anesthesia for Obstetrics*. Baltimore: Williams and Wilkins, 1987; 3–13.
9. Clark RB, Brunner JA. Dopamine for the treatment of spinal hypotension during Cesarean section. *Anesthesiology* 1980; **53**: 514–517.
10. Clark RB, Thompson DS, Thompson CH. Prevention of spinal hypotension associated with Cesarean section. *Anesthesiology* 1976; **45**: 670–674.
11. Coates MB. Combined subarachnoid and epidural techniques. *Anaesthesia* 1982; **37**: 89–90.
12. Coe AJ, Revanas B. Is crystalloid preloading useful in spinal anaesthesia in the elderly? *Anaesthesia* 1990; **45**: 241–243.
13. Cook PR, Malmqvist LA, Bengtsson M, Tryggvason B, Lofstrom JB. Vagal and sympathetic activity during spinal

anaesthesia. *Acta Anaesthesiologica Scandinavica* 1990; **34**: 271–275.

14. Covino BG. Cardiovascular effects of spinal and epidural anaesthesia. *Regional Anaesthesie* 1978; **1**: 23–26.
15. Crawford JS. Experiences with lumbar extradural analgesia for Caesarean section. *British Journal of Anaesthesia* 1980; **52**: 821–824.
16. Cucchiara RF, Restall CJ. Mephenteramine and intravenous fluids for the prevention of hypotension associated with spinal anesthesia. *Anesthesiology* 1973; **39**: 109–110.
17. Datta S, Alper MH, Ostheimer GW, Weiss JB. Method of ephedrine administration and nausea and hypotension during spinal anesthesia for Cesarean section. *Anesthesiology* 1982; **56**: 68–70.
18. Dennison B. Combined subarachnoid and epidural block for Caesarean section. *Canadian Journal of Anaesthesia* 1987; **34**: 105–106.
19. Eckstein KL, Marx GF. Aortocaval compression and uterine displacement. *Anesthesiology* 1974; **40**: 92–96.
20. Ewan A, Macleod DD, Macleod DM, Campbell A, Tunstall ME. Continuous infusion epidural analgesia in obstetrics. A comparison of 0.08% and 0.25% bupivacaine. *Anaesthesia* 1986; **41**: 143–147.
21. Gibbs CP, Werba JV, Banner TE, James CF, Hill CR. Epidural anesthesia: Leg wrapping prevents hypotension. *Anesthesiology* 1983; **59**: A405.
22. Goudie TA, Winter AW, Ferguson DJM. Lower limb compression using inflatable splints to prevent hypotension during spinal anaesthesia for Caesarean section. *Acta Anaesthesiologica Scandinavica* 1988; **32**: 541–544.
23. Greene NM. Area of differential block in spinal anesthesia with hyperbaric tetracaine. *Anesthesiology* 1958; **19**: 45–50.
24. Gutsche BB. Prophylactic ephedrine preceding spinal analgesia for Cesarean section. *Anesthesiology* 1976; **45**: 462–465.
25. Hallworth D, Jellicoe JA, Wilkes RG. Hypotension during epidural anaesthesia for Caesarean section. *Anaesthesia* 1982; **37**: 53–56.
26. Hemmingsen C, Poulson JA, Risbo A. Prophylactic ephedrine during spinal anaesthesia: Double blind study in patients in ASA groups I–III. *British Journal of Anaesthesia* 1989; **63**: 340–342.
27. James FM III, Greiss FC jr, Kemp RA. An evaluation of vasopressor therapy for maternal hypotension during spinal anesthesia. *Anesthesiology* 1970; **33**: 25–34.
28. Kajimoto Y, Nishimura N. Metaraminol and dobutamine for the treatment of hypotension associated with epidural block. *Resuscitation* 1984; **12**: 47–51.
29. Kang YG, Abouleish E, Caritis S. Prophylactic intravenous ephedrine infusion during spinal anesthesia for Cesarean section. *Anesthesia and Analgesia* 1982; **61**: 839–842.
30. Kennedy WF, Sawyer TK, Gerbershagen HU, Everett GB, Cutler RE, Allan GD, Bonica JJ. Simultaneous systematic cardiovascular and haemodynamic measurements during high spinal anaesthesia in normal man. *Acta Anaesthesiologica Scandinavica* 1970; (Suppl. 37): 163–171.
31. Kirno K, Kunimoto M, Lundin S, Elam M, Gunnar-Wallin B. Can galvanic skin response be used as a quantitative estimate of sympathetic nerve activity in regional anesthesia? *Anesthesia and Analgesia* 1991; **73**: 138–142.
32. Koski E, Tuppurainen T, Mattila M, Gordin A, Salo H. Hydroxyethyl starches, dextran and balanced salt solution in correction of hypotension during epidural anaesthesia. *Acta Anaesthesiologica Scandinavica* 1984; **28**: 595–599.
33. Kumar CM. More on combined subarachnoid and epidural techniques. *Anaesthesia* 1986; **41**: 90–91.
34. Lee A, McKeown D, Wilson J. Evaluation of the efficacy of elastic compression stockings in prevention of hypotension during epidural anaesthesia for elective Caesarean section. *Acta Anaesthesiologica Scandinavica* 1987; **31**: 193–195.
35. Lees MM, Scott DB, Kerr MG, Taylor SH. The circulatory effects of recumbant postural change in late pregnancy. *Clinical Science* 1967; **32**: 453–465.
36. Lewis M, Thomas P, Wilkes RG. Hypotension during epidural analgesia for Caesarean section. *Anaesthesia* 1983; **38**: 250–253.
37. Lundberg J, Norgren L, Thomson D, Werner O. Hemodynamic effects of dopamine during thoracic epidural analgesia in man. *Anesthesiology* 1987; **66**: 641–646.
38. McClure JH, Wildsmith JAW. Aspects of spinal anaesthesia. In: Kaufman L, ed. *Anaesthesia: Review 5.* Edinburgh: Churchill Livingstone, 1988; 281.
39. Maclennan FM, Macdonald AF, Campbell DM. Lung water during the puerpurium. *Anaesthesia* 1987; **42**: 141–147.
40. Macleod DM, Tey HK, Byers GF, Dollery WC, Tunstall ME. The loading dose for continuous infusion epidural analgesia. *Anaesthesia* 1987; **42**: 377–381.
41. Malmqvist LA, Bengtsson M, Bjornsson G, Jorfeldt L, Lofstrom JB. Sympathetic activity and haemodynamic variables during spinal analgesia in man. *Acta Anaesthesiologica Scandinavica* 1987; **31**: 467–473.
42. Mathru M, Rao TLK, Kartha RK, Shanmugham M, Jacobs HK. Intravenous albumin administration for prevention of spinal hypotension during Cesarean section. *Anesthesia and Analgesia* 1980; **59**: 655–658.
43. Mattila M, Hannonen P, Puttonen E, Lappalainen S. Dihydroergotamine in the prevention of hypotension associated with extradural anaesthesia. *British Journal of Anaesthesia* 1985; **57**: 976–982.
44. Moya F, Smith B. Spinal anesthesia for Cesarean section. Clinical and biochemical studies of effects on maternal physiology. *Journal of the American Medical Association* 1962; **179**: 609–614.
45. Murray AM, Morgan M, Whitwam JG. Crystalloid versus colloid for circulating preload for epidural Caesarean section. *Anaesthesia* 1989; **44**: 463–466.
46. Nishimura N, Kajimoto Y, Kabe T, Sakamoto A. The effects of volume loading during epidural analgesia. *Resuscitation* 1985; **13**: 31–40.
47. Ockerblad NF, Dillon TG. The use of ephedrine in spinal anesthesia. *Journal of the American Medical Association* 1927; **88**: 1135–1136.
48. O'Keefe N. Epidural analgesia and hypotension. *Anaesthesia* 1991; **46**: 163.
49. Ottesen S, Renck H, Jynge P. Haemodynamic alterations secondary to lumbar epidural analgesia and their modification by plasma expansion and adrenaline administration. *Acta Anaesthesiologica Scandinavica* 1978; (Suppl. 69): 17–31.
50. Parnass SM, Curran MJA, Becker GL. Incidence of hypotension associated with epidural anesthesia using alkalinized and non-alkalinized lidocaine for Cesarean section. *Anesthesia and Analgesia* 1987; **66**: 1148–1150.
51. Peters J, Schlaghecke R, Thouet H, Arndt JO. Endogenous vasopressin supports blood pressure and prevents severe hypotension during epidural anesthesia in conscious dogs. *Anesthesiology* 1990; **73**: 694–702.
52. Rall TW, Schleifer LS. Drugs affecting uterine motility. In: Gilman AG, Goodman LS, Rall TW, Murad F, eds. *Goodman and Gilman's The Pharmacological Basis of Therapeutics.* New York: Macmillan, 1985; 926–945.
53. Ralston DH, Shnider SM, DeLorimer AA. Effects of equipotent ephedrine, metaraminol, mephentermine and methoxamine on uterine blood flow in the pregnant ewe. *Anesthesiology* 1974; **40**: 354–370.
54. Ramanathan S, Grant GJ. Vasopressor therapy for hypotension due to epidural anaesthesia for Caesarean section. *Acta Anaesthesiologica Scandinavica* 1988; **32**: 559–565.
55. Ramanathan S, Masih A, Rock I, Chalon J, Turndorf H. Maternal and fetal effects of prophylactic hydration with crystalloids or colloids before epidural anesthesia. *Anesthesia and Analgesia* 1983; **62**: 673–678.
56. Rawal N, Schollin J, Wesstrom G. Epidural versus combined spinal epidural block for Caesarean section. *Acta Anaesthesiologica Scandinavica* 1988; **32**: 61–66.
57. Reiz S, Nath S, Ponten E. Hemodynamic effects of prenalterol, a b_1 adrenoreceptor agonist, in hypotension induced by high thoracic epidural block in man. *Acta Anaesthesiologica Scandinavica* 1979; **23**: 93–96.
58. Robson S, Hunter S, Boys R, Dunlop W, Bryson M. Changes in cardiac output during epidural anaesthesia for Caesarean section. *Anaesthesia* 1989; **44**: 475–479.
59. Rolbin SH, Cole AFD, Hew EM, Pollard A, Virgint S. Prophylactic intramuscular ephedrine before epidural anaesthesia for Caesarean section: efficacy and actions on the foetus and newborn. *Canadian Anaesthetists Society Journal* 1982; **29**: 148–153.
60. Rout CC, Akoojee SS, Rocke DA, Gouws E. Rapid administration of crystalloid preload does not decrease the

incidence of hypotension after spinal anaesthesia for elective Caesarean section. *British Journal of Anaesthesia* 1992; **68**: 394–397.

61. Sharrock NE, Mineo R, Urquhart B. Hemodynamic response to low-dose epinephrine infusion during hypotensive epidural anesthesia for total hip replacement. *Regional Anesthesia* 1990; **15**: 295–299.
62. Shorten G, Furness G. Diabetes and hypotension. *Anaesthesia* 1990; **45**: 169.
63. Stoelting RK. Allergic reactions during anesthesia. *Anesthesia and Analgesia* 1983; **62**: 341–356.
64. Stone PA, Thorburn J, Lamb KSR. Complications of spinal anaesthesia following extradural block for Caesarean section. *British Journal of Anaesthesia* 1989; **62**: 335–337.
65. Sutter PA, Gamulin Z, Forster A. Comparison of continuous spinal and continuous epidural anaesthesia for lower limb surgery in elderly patients. A retrospective study. *Anaesthesia* 1989; **44**: 47–50.
66. Taivainen T. Comparison of ephedrine and etilefrine for the treatment of arterial hypotension during spinal anaesthesia in elderly patients. *Acta Anaesthesiologica Scandinavica* 1991; **35**: 164–169.
67. Taylor JC, Tunstall ME. Dosage of phenylephrine in spinal anaesthesia for Caesarean section. *Anaesthesia* 1991; **46**: 314–315.
68. Virgilio RW, Rice CL, Smith DE, James DR, Zarins CK, Hobelman CF, Peters RM. Crystalloid *v.* colloid resuscitation: is one better? A randomized clinical study. *Surgery* 1979; **85**: 129–139.
69. Weiner N. Norepinephrine, epinephrine, and the sympathomimetic amines. In: Gilman AG, Goodman LS, Rall TW, Murad F, eds. *Goodman and Gilman's The Pharmacological Basis of Therapeutics*. New York: Macmillan, 1985; 145–180.
70. Wennberg E, Frid I, Haljamae H, Wennergren M, Kjellmer I. Comparison of Ringer's acetate with 3% Dextran 70 for volume loading before extradural Caesarean section. *British Journal of Anaesthesia* 1990; **65**: 654–660.
71. Wollman SB, Marx GF. Acute hydration for prevention of hypotension of spinal anesthesia in parturients. *Anesthesiology* 1968; **29**: 374–380.
72. Wright PMC, Fee JPH. Cardiovascular support during combined extradural and general anaesthesia. *British Journal of Anaesthesia* 1992; **68**: 585–589.

British Journal of Anaesthesia 1993; **70**: 681–683

SHORT COMMUNICATIONS

HAEMODYNAMIC CHANGES IN PATIENTS UNDERGOING LAPAROSCOPIC CHOLECYSTECTOMY: MEASUREMENT BY TRANSTHORACIC ELECTRICAL BIOIMPEDANCE

L. A. H. CRITCHLEY, J. A. J. H. CRITCHLEY AND T. GIN

SUMMARY

Using transthoracic electrical bioimpedance with the BoMed NCCOM3-R7, we measured cardiovascular changes in 16 ASA I and II Chinese patients undergoing laparoscopic cholecystectomy. The peritoneal cavity was insufflated with carbon dioxide to a pressure up to 15 mm Hg. Tidal volume, minute volume and end-tidal carbon dioxide partial pressure were kept constant. Insufflation resulted in a mean (SD) 13 (14)% decrease in stroke index (SI) ($P < 0.01$), but the effect on cardiac index (CI) was more variable (mean 7 (17)% decrease, range 36% decrease to 22% increase ($P = 0.07$)). Mean arterial pressure increased by 55 (29)% ($P < 0.001$) and systemic vascular resistance index increased by 63 (33)% ($P < 0.001$), with the maximum effect occurring 10–15 min after the commencement of insufflation. Multiple regression analysis showed a greater decrease in SI in patients with a small body mass index and large intraperitoneal pressure ($P = 0.01$), while a greater decrease in CI was found in patients with a small body mass index and younger age ($P = 0.001$). Three patients had a further reduction in CI during surgery, with one patient having a 48% decrease compared with pre-induction values. Deflation of the peritoneum resulted in an increase in both CI (25 (26)%) and (22 (29)%) ($P < 0.01$) to values which were not different from pre-induction data. Arterial blood-gas analysis showed decreases in pH and base excess after 1 h of insufflation ($P < 0.01$). (Br. J. Anaesth. 1993; **70**: 681–683)

KEY WORDS

Measurement techniques: transthoracic electrical bioimpedance. Surgery: laparoscopic cholecystectomy.

During laparoscopic gynaecological surgery, insufflation of the peritoneal cavity is usually tolerated well and causes a moderate decrease in cardiac output and an increase in mean arterial pressure [1, 2]. During laparoscopic cholecystectomy, these cardiovascular changes may be greater and more significant because head-up tilt is commonly used, a prolonged period of insufflation is often required and the patients are older, with less cardiopulmonary reserve [3]. We have measured cardiac output non-invasively during laparoscopic cholecystectomy using the BoMed NCCOM3-R7 (BoMed Medical Manufacturing Ltd, Irvine, CA, U.S.A.), which measures beat-to-beat stroke volume using changes in transthoracic electrical bioimpedance [4].

METHODS AND RESULTS

Local Ethics Committee approval and informed consent were obtained. Data were collected from nine male and seven female ASA I or II Chinese patients.

Diazepam 5–10 mg was given 1 h before surgery. Anaesthesia was induced with thiopentone 3–5 mg kg^{-1} and maintained with 0.5% isoflurane and 70% nitrous oxide in oxygen and fentanyl 2–5 µg kg^{-1}. Atracurium was given to facilitate tracheal intubation and maintain neuromuscular block. Normal saline was given i.v. at 5 ml kg^{-1} h^{-1}. The lungs were ventilated with a tidal volume of 10 ml kg^{-1} at 10 b.p.m. End-tidal carbon dioxide partial pressure (PE'_{CO_2}) was maintained at 5.3 kPa using a circle system and varying the gas flow through the carbon dioxide absorber. Fifteen minutes after induction of anaesthesia, the peritoneal cavity was insufflated with carbon dioxide and maintained at a pressure of 11–15 mm Hg throughout the procedure.

The mean arterial pressure (MAP) was measured every 1–3 min (Dinamap 1846SX). The BoMed was connected to the patient using four neck and four lower thoracic electrodes [4]. Stroke index (SI), cardiac index (CI) and heart rate (HR) were recorded continuously. All data were averaged over 16 beats and stored on an IBM-compatible lap-top computer. A 22-gauge radial artery catheter was inserted and blood-gas analysis performed after induction of anaesthesia, after insufflation and at 30-min intervals throughout the procedure. The peak airway pressure, PE'_{CO_2} and intraperitoneal pressure were recorded before and after insufflation, at 10-min intervals during the procedure and after deflation of the peritoneal cavity. Central venous pressure was measured in one patient. Values of 3 mm Hg before induction, 4 mm Hg before insufflation, 10 mm Hg after insufflation and 4 mm Hg after deflation were

---

LESTER A. H. CRITCHLEY, B.MED.SCI., M.B., CH.B., F.F.A.R.C.S.I., TONY GIN, M.D., B.SC., F.R.C.ANAES., F.A.N.Z.C.A. (Department of Anaesthesia & Intensive Care); JULIAN A. J. H. CRITCHLEY, M.B., CH.B., PH.D., F.R.C.P.(EDIN.), (Department of Clinical Pharmacology); Prince of Wales Hospital, The Chinese University of Hong Kong, Shatin, Hong Kong. Accepted for Publication: January 27, 1993.

TABLE I. *Mean* (SD) *values for cardiac index* (*CI*), *stroke index* (*SI*), *heart rate* (*HR*), *mean arterial pressure* (*MAP*) *and systemic vascular resistance index* (*SVRI*) *in 16 patients. A = Awake; B = anaesthetized; C = insufflation; D = laparoscopic surgery; E = after deflation. Significant changes compared with the previous stage:* *P < *0.05;* **P < *0.01*

	A	B	C	D	E
CI (litre min^{-1} m^{-2})	3.47 (0.75)	2.62 (0.48)**	2.38 (0.30)	2.75 (0.78)*	3.33 (0.69)**
SI (cm^3 min^{-1} m^{-2})	46.5 (13.7)	40.9 (7.1)	35.0 (7.0)**	38.9 (11.7)	46.2 (12.3)**
HR (beat min^{-1})	77 (11.6)	65 (9.2)**	69 (9.5)	72 (11.5)	75 (14.2)
MAP (mm Hg)	106 (18.1)	77 (15.6)**	116 (20.6)**	111 (16.8)	107 (184)
SVRI (dyn s cm^{-5} m^{-2})	2356 (802)	2088 (572)	3661 (952)**	3201 (1205)*	2469 (819)**

TABLE II. *Arterial blood-gas analysis after insufflation* (*First*) *and 30 and 60 min later, during laparoscopic cholecystectomy* (*median* (*range*) *or mean* (SD)). *Significant changes compared with First:* *P < *0.05;* **P < *0.01*

	First ($n = 14$)	30 min ($n = 11$)	60 min ($n = 10$)
pH	7.36 (7.23–7.41)	7.36 (7.23–7.37)	7.34 (7.29–7.38)*
Pa_{O_2} (kPa)	20.6 (5.1)	19.1 (4.9)*	16.4 (2.7)**
Pa_{CO_2} (kPa)	6.0 (0.7)	6.0 (0.8)	5.8 (0.7)
Base excess (mmol $litre^{-1}$)	−0.3 (1.8)	−1.3 (2.1)*	−1.8 (1.6)**

used as the best estimate of right atrial pressure (RAP) in the calculation of systemic vascular resistance index (SVRI), where SVRI = 79.9 (MAP − RAP)/CI (dyn s cm^{-5} m^{-2}). Errors in this approximation are small and cause only a small percentage change in (MAP − RAP) and hence SVRI.

The procedure was divided into five stages: awake (5-min period before induction of anaesthesia); anaesthetized (5-min period before insufflation); insufflated (5-min period starting 5 min after insufflation); laparoscopic surgery (20 min after starting insufflation to deflation); deflated (5-min period after deflation). In every patient, the mean values for CI, SI, HR, MAP and SVRI were calculated for each stage. Consecutive means for the five stages were compared using a paired *t* test. Serial arterial blood-gas analysis results were compared by a Wilcoxon signed rank test. The percentage change between the anaesthetized and fully insufflated stages for SI and CI were compared with age, body mass index (BMI = body weight divided by the square of height), peak airway pressure and intraperitoneal pressure using multiple stepwise regression. $P < 0.05$ was considered significant. Results are presented as mean (SD).

The patients were aged 32–78 yr, weights 33–72 kg, heights 141–180 cm and BMI 16.6–25.4 kg m^{-2} (normal range: 19–24 kg m^{-2}).

Induction of anaesthesia caused decreases in CI, HR and MAP (table I). Peak airway pressure was in the range 11–22 cm H_2O (median 17.0 cm H_2O) before insufflation and 13–38 cm H_2O (median 21.5 cm H_2O) during insufflation. Insufflation resulted in a 13 (14)% decrease in (SI), a 55 (29)% increase in MAP and a 63 (33)% increase in SVRI (all $P < 0.01$), but the effect on CI was more variable, ranging from a 36% decrease to a 22% increase. A peak in MAP was seen in all 16 patients, 10–15 min after insufflation and before intraperitoneal surgery started.

The duration of insufflation was 24–130 min (median 55 min). Although CI increased usually during surgery, three patients had a further 15–20% reduction in CI. Deflation was followed by a 25 (26)% increase in CI, a 22 (29)% increase in SI and a 20 (16)% decrease in SVRI (all $P < 0.01$) to values which were not different from the awake values.

Multiple regression analysis showed a greater decrease in SI in patients with a small BMI ($P = 0.005$) and large intraperitoneal pressure ($P = 0.04$) ($r = 0.71$, $P = 0.01$) and a greater decrease in CI in patients with a small BMI ($P = 0.002$) and younger age ($P = 0.007$) ($r = 0.81$, $P = 0.001$).

Progressive acidosis was observed in all patients (table II). PE'_{CO_2} underestimated arterial blood carbon dioxide tension (Pa_{CO_2}) by an average of 0.7 kPa.

One patient, a 33-kg female with untreated hypertension and chronic bronchitis, had a 48% decrease in SI and CI after insufflation compared with awake values. Although insufflation only lasted 24 min, arterial blood-gas analysis at this time showed pH = 7.23, Pa_{O_2} = 26.9 kPa, Pa_{CO_2} = 7.8 kPa and base excess = −3.4 mmol $litre^{-1}$.

COMMENT

The SI decreased with insufflation and multiple regression analysis suggested that increased intra-abdominal pressure was a contributing factor. A detailed study in dogs by Ivankovich [5] showed the decrease to be related to reduced inferior vena cava blood flow. However, increased intrathoracic pressure causing cardiac tamponade and the redistribution of splanchnic blood reserves [2] have also been suggested as possible aetiologies.

The effect of insufflation on CI was less consistent. Motew and colleagues [2] suggested that, in addition to the increased intra-abdominal pressure, other opposing physiological effects such as systemic carbon dioxide uptake and surgical stimulation may be involved.

The increases in MAP and SVRI appeared to be independent of systemic carbon dioxide absorption and surgical stimulation because the maximum increase occurred 10–15 min after insufflation. In dogs, insufflation with nitrous oxide has haemodynamic affects similar to those of carbon dioxide [5]. Patients with massively increased intra-abdominal pressure show similar changes [6]. The increases in MAP and SVRI may be a result of a reflex increase in systemic vascular resistance in response to abdominal distention.

We found that patients with a small BMI experienced a greater decrease in SI and CI after insufflation. This is difficult to interpret and further studies are needed to define which patients are more susceptible to the haemodynamic effects of insufflation.

A progressive, mild metabolic acidosis was noted in all patients and was more marked after only 24 min of insufflation in the patient with a 48% decrease in CI. Similar cases have been reported [1, 3]; in one [3], laparoscopy was aborted after failed attempts to correct the acidosis by increasing ventilation. The acidosis may have been caused partly by a decreased cardiac output with decreased peripheral perfusion and it is possible that increasing ventilation may have depressed cardiac output further. Routine intra-operative monitoring failed to provide evidence of these complications.

We found haemodynamic changes similar to those reported in gynaecological laparoscopy. However, the physiological effects of laparoscopic cholecystectomy appear to be greater.

REFERENCES

1. Lenz RJ, Thomas TA, Wilkins DG. Cardiovascular changes during laparoscopy. *Anaesthesia* 1976; **31**: 4–12.
2. Motew M, Ivankovich AD, Bieniarz J, Albrecht RF, Zahed B, Scommegna A. Cardiovascular effects and acid–base and blood-gas changes during laparoscopy. *American Journal of Obstetrics and Gynecology* 1973; **115**: 1002–1012.
3. Wittgen CM, Andrus CH, Fitzgerald SD, Baudendistel LJ, Dahms TE, Kaminski DL. Analysis of the hemodynamic and ventilatory effects of laparoscopic cholecystectomy. *Archives of Surgery* 1991; **126**: 997–1001.
4. Bernstein DP. Continuous non-invasive real-time monitoring of stroke volume and cardiac output by thoracic electrical bioimpedance. *Critical Care Medicine* 1986; **14**: 898–901.
5. Ivankovich AD, Miletich DJ, Albrecht RF, Heyman HJ, Bonnet RF. Cardiovascular effects of intra-peritoneal insufflation with carbon dioxide and nitrous oxide in the dog. *Anesthesiology* 1975; **42**: 281–287.
6. Cullen DJ, Coyle JP, Teplick R, Long MC. Cardiovascular, pulmonary and renal effects of massively increased intra-abdominal pressure in critically ill patients. *Critical Care Medicine* 1989; **17**: 118–121.

British Journal of Anaesthesia 1993; 70: 684–686

ALTERATIONS IN PAIN THRESHOLD AND PSYCHOMOTOR RESPONSE ASSOCIATED WITH SUBANAESTHETIC CONCENTRATIONS OF INHALATION ANAESTHETICS IN HUMANS

K. TOMI, T. MASHIMO, C. TASHIRO, M. YAGI, M. PAK, S. NISHIMURA, M. NISHIMURA AND I. YOSHIYA

SUMMARY

*We studied the effects of six inhalation anaesthetics at subanaesthetic concentrations of 0.2 MAC on pain threshold and psychomotor function in six healthy volunteers. When compared with 100% oxygen inhalation, nitrous oxide and methyoxyflurane significantly increased pain threshold as measured by a radiant heat algometer, and prolonged the response time to auditory stimuli. In contrast, halothane, enflurane, isoflurane and sevoflurane produced prolongation of the response time to auditory stimuli but did not influence pain perception. The pain threshold with nitrous oxide remained significantly increased 30 min after its discontinuation, while the response time returned to the preinhalation value. We conclude that nitrous oxide and methoxyflurane possess both analgesic and hypnotic actions but halothane, enflurane, isoflurane and sevoflurane do not have an analgesic action at subanaesthetic concentrations, and the analgesic action of nitrous oxide persists after its elimination. (*Br. J. Anaesth. 1993; **70**: 684–686)

KEY WORDS

Anaesthetics, gases: nitrous oxide. Anaesthetics, volatile: methoxyflurane, halothane, enflurane, isoflurane, sevoflurane. Analgesia.

General anaesthesia is a result of both analgesic and hypnotic actions of an anaesthetic agent or a combination of hypnotic and analgesic agents. There has been no study to differentiate the analgesic potency from hypnotic potency of inhalation anaesthetics, because there is no way of differentiating both properties in the anaesthetic concentration range. Although some anaesthetic agents have been demonstrated to cause an increase in pain threshold in subanaesthetic concentrations [1–3], there has been no report that simultaneously evaluated both analgesic and hypnotic actions of inhalation anaesthetics. Therefore, we studied six currently available inhalation anaesthetics at subanaesthetic concentrations in terms of their effects on pain threshold and psychomotor function in normal volunteers.

METHODS AND RESULTS

The study was approved by the Medical Ethics Committee of Osaka University Medical School.

We studied six healthy male volunteers (mean age 37.4 yr, range 29–51 yr; weights 68.3 (SD 13.7) kg) after obtaining informed consent. Each subject was exposed to 100% oxygen and six inhalation anaesthetics at 7-day intervals. The subjects lay comfortably in a supine position for at least 10 min before measurements were made. The anaesthetic gases and oxygen were delivered via an anaesthetic circuit and face mask. End-tidal concentrations of anaesthetics and carbon dioxide were monitored using a Capnomac (Datex). The assessments of analgesic and hypnotic effects were undertaken using 20 trials of the psychomotor test, 25 trials of the pain threshold test and then 20 trials of the psychomotor test. Control, baseline measurements were made while the subject was breathing air via an anaesthetic circuit. After 10 min, one of the following anaesthetics diluted in oxygen 8–10 litre min^{-1} was administered to the subject: methoxyflurane, halothane, isoflurane, enflurane, sevoflurane, nitrous oxide. The end-tidal concentration of each anaesthetic was adjusted to 0.2 MAC equivalent. After the end-tidal concentration was maintained at this value for 20 min, measurements were repeated at the same anaesthetic concentration. Seven series of experiments were performed in random order in a single subject with the six different anaesthetics, plus a control experiment using 100% oxygen.

Pain threshold was assessed using an improved radiant heat algometer (Nakahama Pain Meter NYT-55 (Kudo Electric)) [4]. The thermal output of the algometer was stabilized at a precision of ±1% using a power feedback mechanism. The surface temperature at the site of measurement was maintained constant at 36.5 °C. Five circular sticky tapes

---

KATSUJI TOMI, M.D.; TAKASHI MASHIMO, M.D., PH.D.; CHIKARA TASHIRO, M.D., PH.D.; MASAHARU YAGI, M.D.; MYON PAK, M.D., PH.D.; SHINYA NISHIMURA, M.D., PH.D.; MASAJI NISHIMURA, M.D., PH.D.; IKUTO YOSHIYA, M.D., PH.D.; Department of Anaesthesiology, Osaka University Medical School, Fukushima-ku, Osaka 553, Japan. Accepted for Publication: January 16, 1993.

Correspondence to T. M.

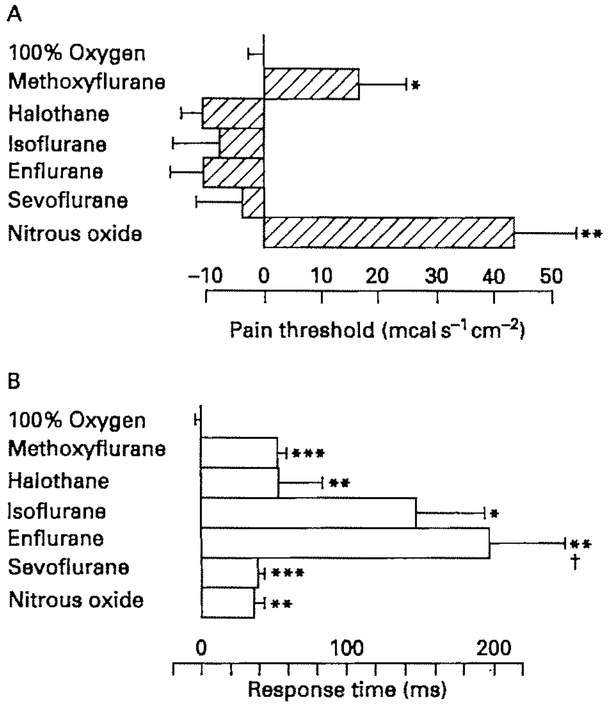


FIG. 1. Differences between values of pain threshold (A) and response time to auditory stimuli (B) measured while the subject breathed air or inhaled oxygen or anaesthetic gases at 0.2 MAC equivalent ($n = 6$) (mean, SE). A: $^{**}P < 0.01$ compared with 100% oxygen, halothane, isoflurane, enflurane and sevoflurane. $^{*}P < 0.05$ compared with 100% oxygen and halothane. B: $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$ compared with 100% oxygen; $^{\dagger}P < 0.05$ compared with methoxyflurane, halothane, sevoflurane and nitrous oxide.

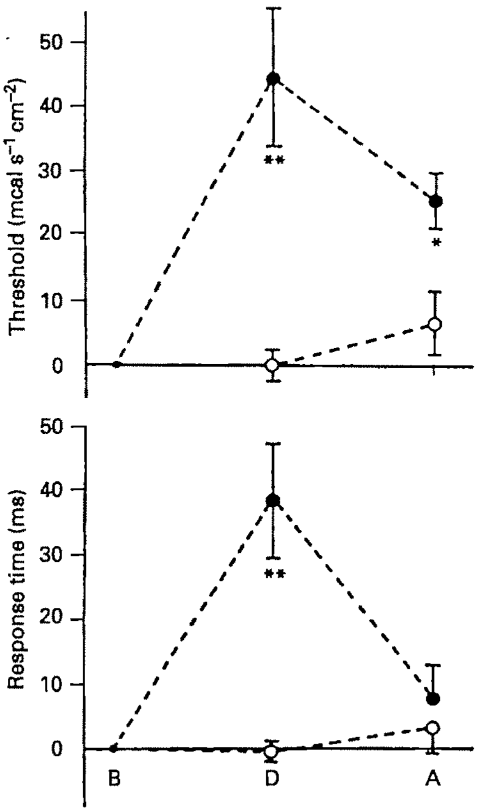


FIG. 2. Mean (SE) residual effects of nitrous oxide on pain threshold and response time ($n = 6$): changes from value before inhalation (B). D = During inhalation; A = 30 min after discontinuation of 100% oxygen (○) or 21% nitrous oxide (●). $^{*}P < 0.05$; $^{**}P < 0.01$ compared with 100% oxygen.

painted black on each side and 18 mm in diameter were stuck to the proximal region of the forearm skin surface. These black spots were subjected, in order, to thermal stimulation by the metal plate of a stimulation head. Pain threshold was determined from the response to thermal stimuli of 3 s duration using the "up-and-down" method [5]: the first stimulus carried a thermal energy of 300 $\mathrm{mcal\ s^{-1}\ cm^{-2}}$; the thermal energy was increased if the stimulus did not cause pain, or decreased after pain. Heat energy was increased or decreased in 20-mcal steps until the sixth exposure, and in 10-mcal steps from the seventh. Heat stimuli were given 25 times at 40-s intervals.

The time elapsed from an auditory stimulus to striking the space key of a personal computer (Nihon Electric Company Ltd, PC 9801 VX) was defined as the response time. The auditory signal was generated by the computer in a random fashion. The frequency of the signal sound used was 1000 Hz and the intervals between sounds varied in the range 1–10 s. Measurements were made 20 times before and 20 times after the pain threshold test. The average value of 40 trails was taken as the response time.

When a subject was given nitrous oxide, additional measurements were performed 30 min after discontinuation of nitrous oxide in oxygen in order to examine any residual effects of the agent.

For statistical analysis, one-way analysis of variance with repeated measures, Dunnett's T test and Tukey's Studentized Range test were used. $P < 0.05$ was considered significant.

Pain thresholds after methoxyflurane and nitrous oxide were significantly greater than in the control group (100% oxygen) (16.3 (23.8) $\mathrm{mcal\ s^{-1}\ cm^{-2}}$ ($P < 0.05$) and 44.2 (27.9) $\mathrm{mcal\ s^{-1}\ cm^{-2}}$ ($P < 0.01$), respectively) (fig. 1A). With the other anaesthetics, pain thresholds did not differ significantly from that in the control group. The pain threshold with nitrous oxide was significantly greater than those with all other anaesthetics tested ($P < 0.01$), with the exception of methoxyflurane. The pain threshold with methoxyflurane was significantly greater than with halothane group ($P < 0.01$).

The response time was increased with all anaesthetics compared with oxygen ($P < 0.01$) (fig. 1B). It was significantly longer with enflurane than with any other anaesthetic, with the exception of isoflurane. With both enflurane and isoflurane, the subjects felt sleepy and three of the subjects intermittently fell asleep.

When tested 30 min after discontinuation of nitrous oxide, the pain threshold remained increased (24.6 (10.7) $\mathrm{mcal\ s^{-1}\ cm^{-2}}$, compared with 6.4 (11.8) $\mathrm{mcal\ s^{-1}\ cm^{-2}}$ with oxygen ($P < 0.05$)) (fig. 2). In contrast, psychomotor reaction time returned to the air-breathing value 30 min after discontinuation of nitrous oxide. There was no significant difference in response time between nitrous oxide (7.6 (13.6) s) and oxygen (3.1 (9.6) s) at this time (fig. 2).

COMMENT

Since the earliest study by Dundee and Moore [1], there have been several studies on analgesic actions of anaesthetic agents. Our data on nitrous oxide correspond well with results reported previously, but our data for methoxyflurane and halothane do not [1–3]. This is the first report on sevoflurane which suggests a lack of analgesic effect.

We found no differences in psychomotor response times when we compared anaesthetic agents with (methoxyflurane and nitrous oxide) and without (halothane and sevoflurane) analgesic property. We also found that enflurane reduced significantly greater response times than halothane or sevoflurane. These data suggest that hypnotic and analgesic properties are MAC determinants, but that the dose–effect relationship is strictly non-linear in terms of hypnotic or analgesic properties, and as a consequence, hypnotic and analgesic data determined, at sub-anaesthetic concentrations of inhalation anaesthetics cannot be extrapolated to MAC values.

We have shown that the analgesic action of nitrous oxide persists after its elimination from the body. This indicates that some analgesic substances may be produced by nitrous oxide *in vivo*. Berkowitz, Ngai and Finck [6] demonstrated that nitrous oxide produced dose-related analgesia and that opioid antagonists reduced its analgesic action in mice. They speculated that nitrous oxide could release endorphins or activate endorphin systems in the central nervous system.

Our data showing no residual effect of nitrous oxide on psychomotor response confirm the results reported by Korttila and colleagues [7], who also found no evidence of tolerance developing to the psychomotor effects of nitrous oxide.

REFERENCES

1. Dundee JW, Love WJ. Alterations in response to somatic pain associated with anaesthesia. XIV: Effects of subnarcotic concentrations of methoxyflurane. *British Journal of Anaesthesia* 1953; **35**: 301–304.
2. Siker ES, Wolfson B, Ciccarelli HE, Telan RA. Effect of subanesthetic concentrations of halothane and methoxyflurane on pain threshold in conscious volunteers. *Anesthesiology* 1966; **28**: 337–342.
3. Robson JG, Davenport HT, Sugiyama R. Differentiation of two types of pain by anesthetics. *Anesthesiology* 1965; **26**: 31–34.
4. Nakahama, H, Yamamoto M. An improved radiant heat algometer and its application to pain threshold measurements in man. *Pain* 1979; **6**: 141–148.
5. Cornsweet TN. The staircase-method in psychophysics. *American Journal of Psychology* 1960; **75**: 485–491.
6. Berkowitz BA, Ngai SH, Finck AD. Nitrous oxide "analgesia": resemblance to opiate action. *Science* 1976; **194**: 967–968.
7. Korttila K, Ghoneim MM, Jacobs L, Mewaldt SP, Petersen RC. Time course of mental and psychomotor effects of 30 per cent nitrous oxide during inhalation and recovery. *Anesthesiology* 1981; **54**: 220–226.

British Journal of Anaesthesia 1993; 70: 687–688

ADRENALINE-INDUCED HYPOTENSION IN NEUROSURGERY

S. PHILLIPS, S. E. HUTCHINSON, P. BAYLY AND T. E. HOLLWAY

SUMMARY

We have compared the effects of scalp infiltration with 0.5% lignocaine, 0.5% lignocaine with adrenaline 1:200000, 0.9% saline and 0.9% saline with adrenaline 1:200000, in a prospective, randomized, double-blind study. Direct arterial pressure, heart rate and bleeding at incision were recorded in 80 patients undergoing craniotomy or craniectomy. Arterial pressure decreased by more than 20% from preinfiltration values in 40% of patients in the saline with adrenaline group, and in 55% of patients in the lignocaine with adrenaline group. It did not decrease in patients who did not receive adrenaline. (Br. J. Anaesth. 1993; **70**: 687–688)

KEY WORDS

Anaesthesia: neurosurgical. Complications: cardiovascular responses. Sympathetic nervous system: beta-adrenergic agonists, subcutaneous adrenaline.

Cerebral perfusion pressure equals mean arterial pressure minus intracranial pressure. In the normal brain, blood supply is maintained constant over a wide range of arterial pressure because of autoregulatory mechanisms [1, 2]. Many neurosurgical patients have increased intracranial pressure and require an increased arterial pressure to ensure cerebral perfusion. Indeed, in those patients whose cerebral autoregulatory mechanisms have been inactivated by disease, cerebral perfusion is dependent on arterial pressure.

In order to reduce bleeding from the scalp and obtund the response to surgical incision, many neurosurgeons routinely infiltrate the subgaleal layer with local anaesthetic and vasoconstrictor; in our institution, 0.5% lignocaine with adrenaline 1:200000 is used. It was noticed that, after this infiltration, a large decrease in arterial pressure occurred, frequently without any change in heart rate. This is in contrast with the hypertensive effect reported previously when solutions containing adrenergic compounds were used [3–5]. The cause for this hypotension, occurring at a relatively uneventful and predictable time during the procedure, was not obvious.

Although the significance of this period of hypotension is unclear, it is conceivable that, in a patient with critical cerebral perfusion, any reduction in arterial pressure may result in cerebral ischaemia. This study was designed to determine which component of the infiltration solution was responsible for hypotension, the frequency and severity of the hypotension, and the effect of different solutions on scalp bleeding.

METHODS AND RESULTS

The study was approved by the Local Medical Ethics Committee and written informed consent was obtained from each patient. We studied 80 neurosurgical patients, aged more than 15 yr and scheduled to undergo craniotomy or craniectomy. The solution used for scalp infiltration was allocated randomly to each patient: group A = 0.9% saline with adrenaline 1:200000 (freshly prepared); group B = 0.5% lignocaine (Antigen); group C = 0.5% lignocaine with adrenaline 1:200000 (Astra); group D = 0.9% saline (Antigen). Neither the anaesthetist nor the surgeon was aware of which solution was used.

All patients received glycopyrronium 0.3 mg i.m. 1 h before operation. Anaesthesia was induced with thiopentone 4–5 mg kg^{-1} and fentanyl 5–10 μg kg^{-1}. Neuromuscular block was produced with vecuronium 0.2 mg kg^{-1} and maintained by infusion. The lungs were ventilated with 66% nitrous oxide and 0–1% isoflurane in oxygen using a Cape Waine ventilator. End-tidal carbon dioxide partial pressures were maintained at 3.5–4.2 kPa. Immediately after induction of anaesthesia, a 20-gauge cannula was inserted into a radial artery and direct arterial pressure measurement commenced using a transducer (Medex) and Cardiocap (Datex) monitor. This was in turn connected to a TOA pen recorder with a paper speed of 20 mm min^{-1}. The transducer and chart recorder were calibrated against a mercury manometer before each use. After transfer to the operating table and a period of haemodynamic stability, the patient was prepared and the scalp infiltrated. The volume of infiltrate used (never more than 20 ml) was at the discretion of the surgeon and thus reflected clinical practice. A hard copy of the arterial pressure trace was made for 2 min before infiltration and continued for a further 5 min.

After raising the skin flap, the surgeon assessed the degree of bleeding as 1 = nil, 2 = minimal, 3 = average, 4 = more than normal, 5 = unacceptable.

STEPHANIE PHILLIPS, B.MED., F.R.C.ANAES.; SUSAN E. HUTCHINSON, M.B., B.S., F.R.C.ANAES.; P. BAYLY*, M.B., B.S., F.R.C.ANAES.; T. E. HOLLWAY; Department of Anaesthetics, Atkinson Morley's Hospital, 31 Copse Hill, Wimbledon, London SW20. Accepted for Publication: December 30, 1992.

*Present address: Brook General Hospital, Shooter's Hill Road, Woolwich, London SE1 4LW.

TABLE I. *Patient data (number of mean (range or* SD*)). Group A = 0.9% saline with adrenaline 1:200000; group B = 0.5% lignocaine; group C = 0.5% lignocaine with adrenaline 1:200000; group D = 0.9% saline*

	Group A ($n = 20$)	Group B ($n = 20$)	Group C ($n = 20$)	Group D ($n = 20$)
Age (yr)	54 (17–80)	48 (25–79)	51 (20–70)	59 (23–71)
Sex (M:F)	11:9	9:11	10:10	10:10
Indication for surgery				
Vascular malformation	7	6	5	7
Space occupying lesion	12	13	15	12
Other	1	1	0	1
Baseline variables				
Heart rate (beat min^{-1})	64 (13)	61 (9)	56 (9)	58 (9)
MAP (mm Hg)	77 (14)	76 (9)	66 (9)	73 (13)

TABLE II. *Number of patients in each group exhibiting a decrease in arterial pressure greater than 20%. (Groups as in table I)*

	Group A	Group B	Group C	Group D
Number of patients	8 (40%)	1 (5%)	11 (55%)	0 (0%)

TABLE III. *Bleeding scores in groups A–D (see table I for definition)*

	Group A	Group B	Group C	Group D
Score				
Nil	4	1	3	2
Minimal	6	3	4	4
Normal	9	9	11	8
Greater than normal	1	5	2	4
Unacceptable	0	2	0	2

At a later date, the arterial pressure traces were assessed from the hard copy by an observer who was unaware of which solution had been used. The systolic and diastolic arterial pressures were noted and the mean arterial pressure calculated ([(systolic − diastolic)/3] + diastolic) every 15 s. The arterial pressure for the 2 min before infiltration was averaged and the number of patients exhibiting a decrease of more than 20% from this value was calculated for each group.

Results for arterial pressure changes were compared using the chi-square test. The effect of adrenaline on bleeding scores was compared using the chi square-test for trend. Patient characteristics and baseline cardiovascular variables were similar in all groups (table I).

A decrease of at least 20% in arterial pressure from values before infiltration occurred in a mean 47.5% of patients receiving adrenaline (groups A and C) and 2.5% of those who did not ($P < 0.001$) (table II). Two patients in group A and two in group C had a decrease of more than 30% from the baseline. The largest reduction (36%) occurred in a patient who had received lignocaine with adrenaline, but there was no significant difference in arterial pressure decrease between groups who did (B, C) or did not (A, D) receive lignocaine ($P = 0.3$).

The average time from infiltration to the smallest recorded pressure was 124 s; mean duration of the trough was 92 s. Heart rate did not vary by more than 10% from baseline in any group, and was similar in all groups.

Bleeding scores as reported by the surgeon were smaller in groups A and C, who received adrenaline ($P < 0.01$) (table III).

COMMENT

Our study has demonstrated that s.c. infiltration of the scalp with solutions containing 1:200000 adrenaline can cause arterial pressure to decrease by more than 20% of baseline values in 47.5% of patients. No change in heart rate occurred. Solutions containing adrenaline reduced surgical bleeding at incision.

It is well known that adrenaline is one of the most potent vasopressors [6] and previous work has been concerned with an increase in arterial pressure [4, 5] associated with its use. It is well known also, however, that small doses of adrenaline (0.1 $\mu g\ kg^{-1}$) may cause the arterial pressure to decrease [6] because of greater sensitivity to adrenaline of vasodilator beta_2 receptors, especially in skeletal muscle beds, than alpha_1 constrictor receptors.

Other possible explanations for the decrease in arterial pressure are unlikely. Myocardial depression by anaesthetic drugs, or vagal response to stretching of the galea, for example, should also have occurred in the saline and lignocaine groups. We did not attempt to relate the dose of adrenaline to body weight, regulate the speed of injection or measure blood concentrations of adrenaline, therefore we cannot say if the effect was dose- or time-related.

Many neurosurgical patients have abnormal cerebral autoregulation and depend on adequate mean arterial pressure for cerebral perfusion. In these patients, a period of hypotension (in our patients for a mean of 92 s) could result in cerebral ischaemia and is undesirable.

REFERENCES

1. Conway CM. Cerebral circulation and brain metabolism. In: *Wylie and Churchill Davidson's A Practice of Anaesthesia*, 5th Edn. London: Lloyd Luke, 1984; 749–751.
2. Michenfelder JD. *Anaesthesia and the Brain*, Chapter 1. Edinburgh: Churchill Livingstone, 1988; 3–12.
3. Muralidhar K, Bhanumurthy S. Attenuation of the cardiovascular responses to subcutaneous adrenaline in neurosurgical patients. *British Journal of Anaesthesia* 1992; **68**: 264–267.
4. Christensen KN, Jensen JK, Sogaard I. Blood pressure response to administration of local anaesthetics with noradrenaline in craniotomies. *Acta Neurochirurgica* 1980; **51**: 157–160.
5. Campkin TV, Turner JM. *Neurosurgical Anaesthesia and Intensive Care*, Chapter 9. London: Butterworths, 1980; 134.
6. Goodman A, Gilman A, Rall TW, Nies AS, Taylor P (eds). *Goodman and Gilman's The Pharmacological Basis of Therapeutics*, 8th Edn. London: Pergamon Press, 1990; 192–193.

British Journal of Anaesthesia 1993; **70**: 689–690

SHUNT FLOW AND CAVAL PRESSURE GRADIENT DURING VENO–VENOUS BYPASS IN HUMAN ORTHOTOPIC LIVER TRANSPLANTATION

R. U. SCHERER, R. M. GIEBLER, M. J. SCHMUTZLER, F. M. GÜNNICKER AND W. J. KOX

SUMMARY

The routine use of veno–venous bypass during the anhepatic phase of orthotopic liver transplantation is controversial. Decreased shunt flows (1.5–3.0 litre min^{-1}), as reported in the literature, may explain the lack of beneficial effects on outcome. We have studied the influence of bypass flows on caval pressure gradient (CPG) and renal perfusion pressure (RPP) in 45 patients undergoing orthotopic liver transplantation using a portofemoro–subclavian veno–venous bypass system. Mean shunt flow was 3.63 litre min^{-1}. Second-order polynomial regressions best described the relationship between shunt flow and CPG ($r = 0.674$), RPP ($r = 0.727$), and cardiac output ($r = 0.602$). Shunt flows less than 3.0 litre min^{-1} failed to normalize CPG and RPP, whereas flows greater than 5.0 litre min^{-1} did not substantially improve haemodynamic state. (Br. J. Anaesth. 1993; **70**: 689–690)

KEY WORDS

Liver: blood flow. Surgery: Liver transplantation.

There is no evidence that extracorporeal veno–venous bypass during orthotopic liver transplantation is beneficial [1] as far as outcome is concerned [2]; however, improvement in such physiological variables as cardiac output and urine production has been demonstrated [2].

Shunt flows described in the literature range from 1.5 to 3.0 litre min^{-1} in adults [2–4]. It is not known if such flows are sufficient to normalize haemodynamic pressures and thus cardiac output. Therefore, we have assessed the efficacy of shunt flow during portofemoro–subclavian bypass by measuring infra- (ICAVP) to suprahepatic (SCAVP) caval pressure gradient (CPG) and mean arterial pressure (MAP), from which renal perfusion pressure (RPP = MAP − ICAVP) was derived.

METHODS AND RESULTS

After obtaining local Ethics Committee approval and written, informed consent, we studied the efficacy of portofemoro–subclavian bypass in 45 consecutive adult patients (23 male) undergoing elective or emergency orthotopic liver transplantation. Adults with a body weight less than 50 kg were excluded. Median age was 42 yr (range 19–65 yr) and median body surface area 1.84 m^2 (range 1.34–2.28 m^2). Thirty patients were classified Child B, and 15 Child C; nine were "high urgent" (Eurotransplant urgency code HU) because of fulminant hepatic failure.

General anaesthesia was maintained by a continuous infusion of propofol 40–60 μg kg^{-1} min^{-1} and fentanyl 0.1–0.3 μg kg^{-1} min^{-1} with 0.4–0.6% isoflurane. Fluid administration, blood transfusion and catecholamine support were adjusted to produce a normal haemodynamic state with a mean arterial pressure > 60 mm Hg, central venous pressure 5–10 mm Hg, cardiac index > 2.5 litre min^{-1} m^{-2}, haemoglobin concentration 10 g litre^{-1} and PCV 30%. All patients received low-dose dopamine 3–5 μg kg^{-1} min^{-1}. In six urgent cases, adrenaline 0.1–0.3 μg kg^{-1} was given to maintain cardiac output. ICAVP was measured via the right femoral vein.

Before operation, the left femoral and subclavian veins were cannulated with 7-mm single lumen catheters (LAUB percutaneous cannulation set, Cook Europe, Mönchengladbach, Germany) for portofemoro–subclavian bypass. Shunt flows were initially rendered optimum by adjusting the pump speed to the greatest possible flow rate before collapse of the tubing.

When shunt flow reached a steady state during the anhepatic phase, haemodynamic measurements were performed. Cardiac index (CI), oxygen transport ($D\text{o}_2$) and oxygen consumption ($\dot{V}\text{o}_2$) were derived using the usual equations. Statistical analysis was performed by linear and second order polynomial regression analysis. The significance of sample correlation coefficient (r) was calculated using a two-tailed t test. $P < 0.05$ was considered significant.

Mean shunt flow was 3.63 (SEM 0.20) litre min^{-1} (range 0–6.6 litre min^{-1}). In one patient it was not possible to establish a shunt flow because of air entrainment into the portal cannula. Mean haemo-

---

R. U. SCHERER*, M.D.; R. M. GIEBLER, M.D.; M. J. SCHMUTZLER, M.D.; F. M. GÜNNICKER, M.D.; W. J. KOX, M.D., PH.D.; Department of Anaesthesiology, University Hospital Essen, D-4300 Essen 1, Germany. Accepted for Publication: January 23, 1993.

*Address for correspondence: Institut für Anästhesiologie, Universitätsklinikum der GHS Essen, Hufelandstraße 55, D-4300 Essen 1, F.R.G.

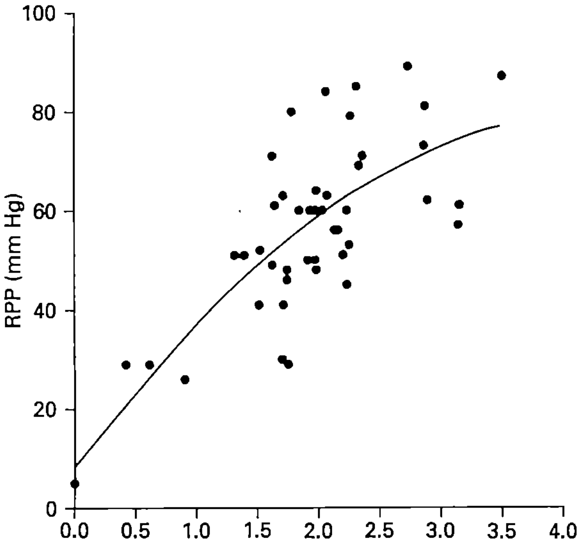


FIG. 1. Relationship between shunt flow index (SFLI) and renal perfusion pressure (RPP): $y = 8.22+32.02x-3.82x^2$. $r = 0.744$, $P < 0.0005$.

globin concentration was 9.9 (1.5) g litre^{-1} before onset of veno–venous bypass and 10.2 (0.26) g litre^{-1} during shunt; PCV was 29.2 (0.69)% and 30.0 (0.98)%, respectively.

During veno–venous bypass, CI was 3.82 (0.16) litre min^{-1} m^{-2} (4.41 (0.2) litre min^{-1} m^{-2} before bypass); MAP was 74.9 (2.3) mm Hg (77.7 (1.9) mm Hg before bypass); CPG was 6.8 (0.8) mm Hg (7.5 (1.2) mm Hg before bypass) RPP was 56.4 (2.7) mm Hg (62.4 (1.9) mm Hg before bypass); PAP was 17.5 (0.7) mm Hg (18.1 (0.9) mm Hg before bypass), PAOP was 8.9 (1.2) mm Hg (11.7 (1.0) mm Hg before bypass); $D\text{O}_2$ was 491.6 (26.7) ml min^{-1} m^{-2} (549.2 (26.5) ml min^{-1} m^{-2} before bypass) and $\dot{V}\text{O}_2$ was 115.7 (7.8) ml min^{-1} m^{-2} (124.3 (3.9) ml min^{-1} m^{-2} before bypass).

The relationship between shunt flow and CPG was characterized best by a second-order polynomial regression ($y = 22.78-7.19x+0.68x^2$; $r = 0.674$, $P < 0.0005$). Taking into account the patient's body surface area by correlating the CPG and RPP to shunt flow index, an even better correlation with CPG ($r = 0.66$, $P < 0.0005$) and RPP ($r = 0.744$, $P < 0.0005$) was found (fig. 1).

As far as the relationship between shunt flow and CPG or RPP was concerned, we found no differences between patients with chronic and acute hepatic failure.

The relationship between shunt flow and $D\text{O}_2$ was characterized by a second-order polynomial regression ($y = 98.11+3.72x-0.13x^2$; $r = 0.329$, $P < 0.05$). ICAVP and $\dot{V}\text{O}_2$ showed an inverse relationship (second-order polynomial regression $y = 38.11+3.72x-0.13x^2$; $r = 0.329$, $P < 0.05$).

COMMENT

Our study has shown that the use of a 7-mm percutaneous cannulation set for catheterization of the subclavian and femoral veins for portofemoro–subclavian bypass ensures large shunt flows (mean 3.6 litre min^{-1}). The data indicate that CPG and hence RPP were dependent on shunt flow and that this relationship was almost linear for a shunt flow less than 3 litre min^{-1}. The correlation between shunt flow and CO ($r = 0.602$, $P < 0.0005$) in our patients was good, as were the correlations between shunt flow and RPP ($r = 0.675$, $P < 0.0005$) or CPG ($r = 0.571$, $P < 0.0005$), respectively. ICAVP and hence CPG and RPP were dependent mainly on shunt flow and thus mirrored the efficacy of blood drainage from the portocaval to the superior caval venous system.

If orthotopic liver transformation is performed without veno–venous bypass RPP is usually small, leading to intraoperative oliguria [1]. Estrin and colleagues [5] found a mean RPP between 40 and 49 mm Hg in 26 adult patients without veno–venous bypass and the CPG was 36–37 mm Hg. In that group of patients, mean arterial pressure during the anhepatic phase was surprisingly increased and even greater (82–98 mm Hg) than in the pre-anhepatic phase (81–91 mm Hg), probably because of fluid and catecholamine administration.

Adverse haemodynamic changes associated with cross clamping of the caval vein can be overcome by volume loading [5] without major complications [1] such as fluid overload. Even with veno–venous bypass, this remains a major problem and has led to the institution of intraoperative continuous arteriovenous haemofiltration in some centres [6].

Our study shows that shunt flows less than 3.0 litre min^{-1} failed to normalize CPG and RPP. Our data show that the relationship between shunt flow index and CI, CPG and RPP behaved in a curvilinear fashion and that an increase in shunt flows led to an increase in RPP and a decrease of CPG linearly when shunt flows were decreased (< 3.5 litre min^{-1}) but optimized CPG (< 5 mm Hg) and RPP (> 60 mm Hg) to only a small extent when shunt flows were great (> 5 litre min^{-1}).

REFERENCES

1. Wall WJ, Grant DR, Duff JH, Kutt JL, Ghent CN, Bloch MS. Liver transplantation without venous bypass. *Transplantation* 1987; 43: 56–61.
2. Shaw BW, Martin DJ, Marquez JM, Kang YG, Bugbee AC, Iwatsuki S, Griffith BP, Hardesty RL, Bahnson HT, Starzl TE. Venous bypass in clinical liver transplantation. *Annals of Surgery* 1984; 200: 524–534.
3. Kang YG, Freeman JA, Aggarwal S, De Wolf AM. Hemodynamic instability during liver transplantation. *Transplantation Proceedings* 1989; 21: 3489–3492.
4. Paulsen AW, Whitten CW, Ramsay MAE, Klintmalm GB. Considerations for anesthetic management during veno–venous bypass in adult hepatic transplantation. *Anesthesia and Analgesia* 1989; 68: 489–496.
5. Estrin JA, Belani KG, Ascher NL, Lura D, Payne W, Najarian JS. Hemodynamic changes on clamping and unclamping of major vessels during liver transplantation. *Transplantation Proceedings* 1989; 21: 3500–3505.
6. Tuman KJ, Spiess BD, McCarthy RJ, Logas WG, Williams JW, Sankary HN. Effects of continuous arteriovenous hemofiltration on cardiopulmonary abnormalities during anesthesia for orthotopic liver transplantation. *Anesthesia and Analgesia* 1988; 67: 363–369.

British Journal of Anaesthesia 1993; **70**: 691–693

TRACHEAL TUBE CUFF INFLATION AS AN AID TO BLIND NASOTRACHEAL INTUBATION

A. C. VAN ELSTRAETE, J. H. PENNANT, N. M. GAJRAJ AND R. A. VICTORY

SUMMARY

We have assessed the efficacy of tracheal tube cuff inflation in the oropharynx as an aid to blind nasotracheal intubation in 20 ASA I and II patients undergoing elective oral surgery. The trachea was intubated once using the technique of tracheal tube cuff inflation in the oropharynx and once keeping the tracheal tube cuff deflated throughout the manoeuvre. With the cuff deflated, intubation was successful in nine of 20 (45%) patients; in eight of 20 (40%) it was successful on the first attempt. With the tracheal tube cuff inflated, intubation was successful in 19 of 20 patients (95%), 15 of 20 (75%) of these on the first attempt. The success rates were significantly different ($P < 0.01$*). Times to intubate were not significantly different (*$P > 0.05$*). We conclude that, in normal patients, tracheal tube cuff inflation in the oropharynx increases the success rate of blind nasotracheal intubation.* (Br. J. Anaesth. 1993; **70**: 691–693)

KEY WORDS
Intubation: blind nasotracheal.

Blind nasotracheal intubation is a useful technique, although malpositioning results in variable success rates. Several manoeuvres have been described in order to avoid this problem. Inflation of the tracheal tube cuff has been described in a case report as an aid to blind nasotracheal intubation [1], although its efficacy has not been assessed formally. This prospective, randomized study was designed to determine if tracheal tube cuff inflation in the oropharynx improves the success rate of blind nasotracheal intubation in normal, paralysed patients.

METHODS AND RESULTS

After Institutional Review Board approval, informed written consent was obtained from 20 ASA I and II patients scheduled to undergo elective oral surgery requiring nasotracheal intubation. Patients with airway abnormalities such as tracheal deviation were excluded.

After premedication with ranitidine 150 mg and sodium citrate 30 ml orally, and after preoxygenation for 3 min, anaesthesia was induced with thiopentone 5 mg kg^{-1} and fentanyl 2 $\mu g\ kg^{-1}$ i.v. Neuromuscular block was produced with vecuronium 0.1 mg kg^{-1} and monitored using a peripheral nerve stimulator. Additional intraoperative monitoring consisted of electrocardiography, capnography, finger pulse oximetry and non-invasive automated arterial pressure measurement. Arterial pressure was recorded at 1-min intervals.

The patient's lungs were ventilated with 1% isoflurane in oxygen using a face mask until complete muscle paralysis was demonstrated using the nerve stimulator. Patients were positioned supine with the head placed in the "sniffing" position before intubation. A size 7.0- or 8.0-mm polyvinylchloride cuffed tracheal tube was selected according to the patient's weight. The distance from the nostril to the oropharynx was estimated by aligning the tracheal tube against the side of the patient's face before intubation. The tracheal tube was then introduced via the right nostril and advanced until there was a loss of resistance and the tip was positioned in the oropharynx.

The trachea was intubated blindly by a junior resident, once using the technique of cuff inflation and once keeping the cuff deflated throughout the manoeuvre. The order of intubation was determined using a table of random numbers. The times taken to intubate the trachea and the number of attempts and failures were recorded for each procedure.

The tracheal tube cuff was inflated in the oropharynx using 15 ml of air [1] and then advanced gently by the anaesthetist until slight resistance was felt as the inflated cuff made contact with the vocal cords. At that time it was deflated and the tracheal tube advanced into the trachea, whereupon the cuff was reinflated (fig. 1).

The time taken to intubate the trachea was measured from the moment the anaesthetist held the tracheal tube with its tip already positioned in the oropharynx, until correct tracheal placement was confirmed by an end-tidal carbon dioxide partial pressure greater than 3.3 kPa.

After satisfactory insertion of the tracheal tube, the patient's lungs were ventilated manually for 1 min. The tube was then withdrawn to its pharyngeal position and the same anaesthetist intubated the trachea using the second technique.

A. C. VAN ELSTRAETE, M.D.; J. H. PENNANT, F.R.C.ANAES.; N. M. GAJRAJ, F.R.C.ANAES.; R. A. VICTORY, F.F.A.R.C.S.I.; Department of Anesthesiology and Pain Management, The University of Texas Southwestern Medical Center, 5323 Harry Hines Boulevard, Dallas, Texas 75235-9068. U.S.A. Accepted for Publication: January 21, 1993.

Correspondence to N.M.G.

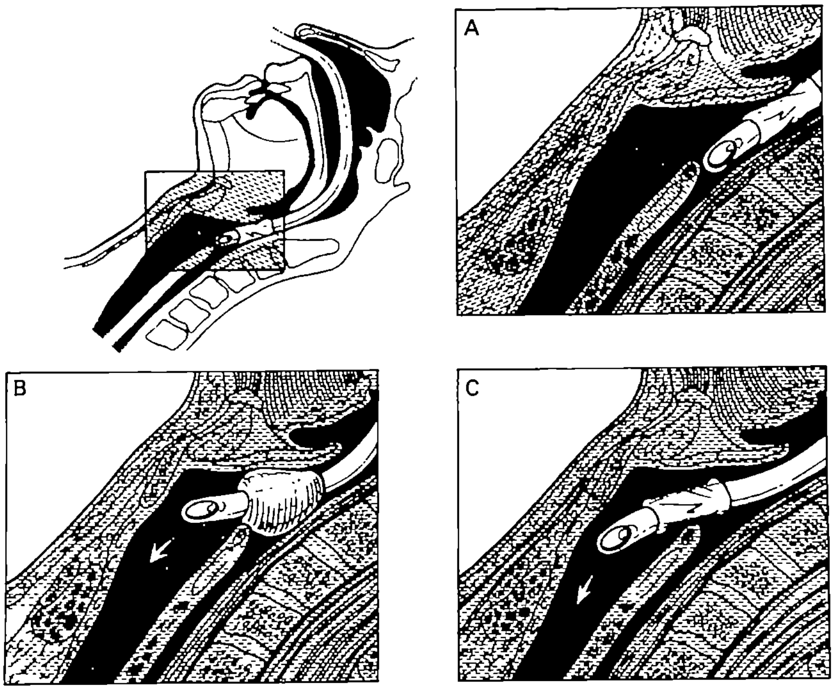


FIG. 1. Technique of tracheal tube (TT) cuff inflation in the oropharynx for blind nasotracheal intubation. A: The tip of the TT is positioned in the oropharynx. B: The cuff is inflated using 15 ml of air and the TT is advanced until the cuff contacts the vocal cords. C: The cuff is deflated and the TT is advanced into the trachea.

A maximum of three attempts was allowed for each intubation. If at any time the arterial oxygen saturation decreased to less than 90% or if cardiovascular variables changed more than 20% from baseline values, the procedure was abandoned, the patient excluded from the study and intubation performed using direct laryngoscopy. If the first procedure failed three times, the second procedure was performed. If the second procedure failed three times, the trachea was intubated using direct laryngoscopy.

Data were expressed as mean (SD) and analysed using the chi-square and paired Student's t tests as appropriate. $P < 0.05$ was considered significant.

Two of the patients were female and 18 male. Their ages ranged from 18 to 60 yr (mean 34 yr), their weights from 57 to 92 kg (mean 72 kg). Intubation was successful in nine of 20 patients (45%) when the tracheal tube cuff was kept deflated throughout, and in 19 of 20 patients (95%) using the technique of tracheal tube cuff inflation in the oropharynx. This difference in success rates was statistically significant ($P < 0.01$). Intubation was unsuccessful in one patient using both techniques. Mean times to intubate were 22.3 (10.9) s with the cuff deflated and 26.2 (15.0) s with the cuff inflated. This difference was not statistically significant ($P > 0.05$). Success on the first attempt at intubation occurred in eight of 20 subjects (40%) with the cuff deflated, but in 15 of 20 subjects (75%) when the tracheal tube cuff was inflated in the oropharynx.

COMMENT

Blind nasotracheal intubation was first described by Magill in spontaneously breathing patients using breath sounds as a guide to placement [2], and still remains a useful technique. In certain circumstances, such as pharyngeal bleeding, it may be preferable to fibreoptic intubation [3].

However, misplacement of the tracheal tube is a problem. It may become positioned in the oesophagus, on the anterior commissure of the larynx, in the vallecula or in the pyriform fossa. Techniques for aiding correct placement other than listening for breath sounds include flexion, extension or rotation of the neck, rotation of the tracheal tube and digital manipulation of the larynx [4]. Also, a fibreoptic bronchoscope may be passed through the tube [5].

We have shown that tracheal tube cuff inflation in the oropharynx is effective in improving the success rate of blind nasotracheal intubation in paralysed patients.

In the presence of normal pharyngeal anatomy, inflation of the tracheal tube cuff in the oropharynx is assumed to centre the tip of the tube and to direct it anteriorly towards the larynx. As a result, misplacement of the tracheal tube into the oesophagus or pyriform fossa may be avoided. Cuff inflation in the oropharynx could theoretically traumatize the upper respiratory tract. We did not perform postoperative laryngoscopy, but believe that cuff inflation would cause less trauma than multiple attempts at intubation. This technique does not require any additional equipment or manipulation of the head or neck and may be useful in cases of cervical spine trauma or immobility. It remains to be established if this technique improves the success rate of blind nasotracheal intubation in cases of difficult intubation. Further controlled studies in this area would be valuable.

REFERENCES

1. Gorback MS. Inflation of the endotracheal tube cuff as an aid to blind nasotracheal intubation. *Anesthesia and Analgesia* 1987; **66**: 917.

2. Magill IW. Techniques in endotracheal anaesthesia. *British Medical Journal* 1930; **2**: 817.
3. Collins PD, Godkint RA. Awake blind nasotracheal intubation. A dying art? *Anaesthesia and Intensive Care* 1992; **20**: 225–227.
4. Atkinson RS, Rushman GB, Lee JA. *A Synopsis of Anaesthesia*, 10th Edn. Bristol: Wright, 1987; 208–210.
5. Messiter KH, Patterson, KI. Endotracheal intubation with the fibre-optic bronchoscope. *Anaesthesia* 1980; **35**: 294–298.

British Journal of Anaesthesia 1993; 70: 694–695

POTENCY ESTIMATION OF MIVACURIUM: COMPARISON OF TWO DIFFERENT MODES OF NERVE STIMULATION

V. R. MADDINENI, R. K. MIRAKHUR, R. COOPER AND E. McCOY

SUMMARY

*We have assessed the potency of mivacurium, a new non-depolarizing neuromuscular blocker, using two different modes of nerve stimulation in patients anaesthetized with thiopentone, fentanyl and nitrous oxide in oxygen. The force of contraction of adductor pollicis was measured after single twitch stimulation at 0.1 Hz or train-of-four stimulation (TOF) at 2 Hz every 10 s. Dose–response curves were constructed using a single-dose method for each mode of stimulation. The ED_{50} and ED_{95} were 43 μg kg^{-1} and 83 μg kg^{-1}, respectively, for the single twitch responses and 34 μg kg^{-1} and 66 μg kg^{-1}, respectively, for the first response of the TOF stimulation. The difference between the ED_{95} doses was not significant (*P *= 0.051), but the difference between the ED_{50} doses was significant (*P *= 0.03), suggesting greater sensitivity of the neuromuscular junction using TOF stimulation. The results show that the information obtained using single twitch stimulation at 0.1 Hz is not the same as that obtained from the first response of the TOF stimulation.* (Br. J. Anaesth. 1993; **70**: 694–695)

KEY WORDS

Neuromuscular relaxants: mivacurium. Monitoring: single twitch, train-of-four.

Mivacurium chloride is a recently-developed non-depolarizing neuromuscular blocking drug with a relatively short duration of action because of its breakdown by plasma cholinesterase [1].

Previous studies with other neuromuscular blockers have shown that the mode of stimulation influences their estimated potency, the train-of-four (TOF) mode of stimulation at 2 Hz being associated with smaller ED_{95} values compared with single twitch stimulation at 0.1 or 0.15 Hz [2, 3]. In the present study, we have estimated the potency of mivacurium using two different modes of nerve stimulation.

METHODS AND RESULTS

We studied 60 ASA I or II patients aged 18–65 yr with their written informed consent and approval from the Regional Medical Ethics Committee. They were anaesthetized with thiopentone 3–5 mg kg^{-1}, fentanyl 1–3 μg kg^{-1} and nitrous oxide in oxygen and further increments of fentanyl, thiopentone, or both, as required. Ventilation of the lungs was assisted to maintain an end-tidal carbon dioxide concentration at 4.5–5.0%.

The ulnar nerve was stimulated percutaneously at the wrist using supramaximal stimuli of 0.2 ms duration and the resultant force of contraction of the adductor pollicis muscle recorded using a force displacement transducer and a neuromuscular function analyser (Myograph 2000, Biometer Ltd). After stabilization of the control responses, six patients each were allocated randomly to receive mivacurium 20, 40, 60, 80 or 100 μg kg^{-1} and to be stimulated in a single twitch mode at 0.1 Hz or in a TOF mode at

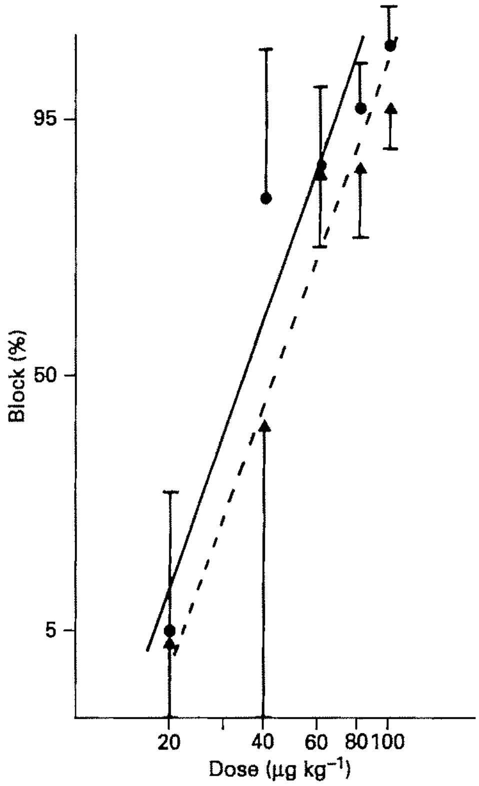


FIG. 1. Dose–response curves for mivacurium using the single twitch (▲--▲) and the train-of-four modes of stimulation (●—●). Individual points represent mean (SD).

V. R. MADDINENI, M.D., F.F.A.R.C.S.I.; R. K. MIRAKHUR, M.D., F.R.C.ANAES., F.F.A.R.C.S.I.; R. COOPER, F.F.A.R.C.S.I.; E. MCCOY, F.F.A.R.C.S.I.; Department of Anaesthetics, The Queen's University of Belfast, Whitla Medical Building, 97 Lisburn Road, Belfast BT9 7BL. Accepted for Publication: December 21, 1992.
Correspondence to R.K.M.

2 Hz every 10 s and the maximum depression of twitch height (single twitch) or of the first response in the TOF (T1) was then recorded. We used a single dose technique as described previously for neuromuscular blockers with relatively short duration of action [4].

The twitch height data were subjected to arc-sine transformation as described previously [4] for responses involving the extreme points (0 and 100 %) on the dose–response curves. Regression analysis of the data was performed, dose–response curves constructed for each mode of stimulation and the values of ED_{50} and ED_{95} estimated. These were tested for statistical significance ($P < 0.05$) using Student's *t* test.

The patients in each of the five groups within each mode of stimulation were comparable in age, weight and height. The degree of block attained increased in a dose-related manner, varying from 4 % and 5 % with the single twitch and TOF modes, respectively, after mivacurium 20 $\mu g\ kg^{-1}$, to 97 % and 99 %, respectively, after mivacurium 100 $\mu g\ kg^{-1}$.

The dose–response curves (fig. 1) showed that the TOF mode of stimulation was associated with a greater degree of block. However, there was no significant difference between the slopes. The calculated values of both the ED_{50} and the ED_{95} were smaller with the TOF mode of stimulation. The ED_{50} values of 43 $\mu g\ kg^{-1}$ and 34 $\mu g\ kg^{-1}$ with single twitch and TOF modes of stimulation, respectively, differed significantly ($P = 0.03$). ED_{95} values were 83 $\mu g\ kg^{-1}$ and 66 $\mu g\ kg^{-1}$ with the single twitch and TOF modes of stimulation, respectively. The differences between the groups with the ED_{95} dose, however, failed to attain statistical significance ($P = 0.051$).

COMMENT

We have shown that the mode of stimulation affected the dose–response curve and apparent potency of mivacurium chloride; TOF stimulation produced apparently greater potency. ED_{50} values were significantly different ($P = 0.03$), whereas ED_{95} values just failed to attain statistical significance ($P = 0.051$). This may reflect relatively large individual variability among the patients in response to neuromuscular blocking drugs. In these respects, mivacurium behaves similarly to atracurium and rocuronium [2, 3]. The estimates of potency in the present study are similar to those described by others who used comparable modes of stimulation.

The apparently greater sensitivity using TOF stimulation may result from increased muscle blood flow, as has been suggested for the earlier onset of neuromuscular block using this mode of stimulation [5]. It may be possible also that the more rapid rates of stimulation used in the TOF mode induced muscle fatigue and diminished the responsiveness of the stimulated muscle in the presence of a neuromuscular blocking agent, as the stimulus frequency has been shown to reduce both the dose of blocking drug required and the time for onset of a given degree of neuromuscular block [6]. The present study supports the contention that it is important and relevant to state the method of stimulation used when comparing potencies of different myoneural blockers [2]. From a clinical point of view, it is probably preferable to use the dose (or multiples of it) estimated using the single twitch mode, as it is a more reliable index of neuromuscular block for procedures such as tracheal intubation [6].

ACKNOWLEDGEMENT

Supplies of mivacurium and financial assistance were received from the Wellcome Foundation.

REFERENCES

1. Savarese JJ, Ali HH, Basta SJ, Embree PB, Scott RPF, Sunder N, Weakly JN, Wastila WB, El-Sayad HA. The clinical neuromuscular pharmacology of mivacurium chloride. *Anesthesiology* 1988; **68**: 723–732.
2. Cooper RA, Mirakhur RK, Elliott P, McCarthy GJ. Estimation of the potency of Org 9426 using two different modes of nerve stimulation. *Canadian Journal of Anaesthesia* 1992; **39**: 139–142.
3. Ali HH, Basta SJ, Savarese JJ, Gargarian M, Scott RPF, Sunder N, Gionfriddo M. Single twitch and train-of-four responses for atracurium and vecuronium. *Anesthesia and Analgesia* 1985; **64**: 187.
4. Gibson FM, Mirakhur RK, Lavery GG, Clarke RSJ. Potency of atracurium: a comparison of single dose and cumulative dose techniques. *Anesthesiology* 1985; **62**: 657–659.
5. Curran MJ, Donati F, Bevan DR. Onset and recovery of atracurium and suxamethonium-induced neuromuscular blockade with simultaneous train-of-four and single twitch stimulation. *British Journal of Anaesthesia* 1987; **59**: 989–994.
6. Ali HH, Savarese JJ. Stimulus frequency and dose–response curve to d-tubocurarine in man. *Anesthesiology* 1980; **52**: 36–39.

British Journal of Anaesthesia 1993; 70: 696–698

CASE REPORT

A BIFURCATED ENDOBRONCHIAL TUBE IN THE MANAGEMENT OF LARYNGOTRACHEO-OESOPHAGEAL CLEFT REPAIR

R. AHMAD, K. A. SAMI AND A. RABEEAH

SUMMARY

We describe the management of laryngotracheo-oesophageal cleft Type III using a bifurcated endobronchial tube. When the cleft was opened for repair, we were able to obtain effective control of the airway, which is the main problem in this rare congenital anomaly. Commercial tubes are not available, so we made the tube on the day of surgery, immediately before operation. (Br. J. Anaesth. 1993; **70**: 696–698)

KEY WORDS
Equipment: endobronchial tube. Anaesthesia: paediatric. Surgery: laryngotracheo-oesophageal fistula.

Laryngotracheo-oesophageal cleft (LTEC) is a rare congenital anomaly with a high mortality rate resulting from delay in diagnosis and chronic aspiration [1]. More than 170 cases have been reported in the literature [2]. In a classification devised by Pettersen [3], Type I LTEC involves the larynx, Type II extends to the 6th tracheal ring, (corresponding to the cervical trachea) and Type III lesions extend to the carina. Type IV lesions have been described recently and may extend into one or both mainstem bronchi [4]. The anaesthesia literature contains few references to anaesthetic management of these patients, but describes the incidence, symptomatology and embryology of LTEC [5], anaesthesia for endoscopic procedures in Type I lesions [6], difficult intubation in a neonate with associated tracheal stenosis [7] and one patient with a staged repair of an extensive cleft [8]. We have recently used a bifurcated endobronchial tube as suggested in the surgical literature [9], for a combined cervical and thoracic approach for the repair of a Type III cleft in a neonate.

CASE REPORT

A 1-month-old baby girl was admitted to our Hospital with a referral diagnosis of tracheo-oesophageal fistula. She was born in a district hospital and developed respiratory distress after oral feeding.

On admission, the baby was found to be cyanotic, despite receiving 100 % oxygen. Chest x-ray showed bilateral infiltrates and areas of atelectasis more pronounced in the right chest. Oesophageal contrast studies revealed the presence of a laryngotracheo-oesophageal cleft down to the carina. Other congenital anomalies were not found. A nasogastric tube was passed, with some difficulty, to decompress the stomach and i.v. fluids were given. The patient was brought to the operating theatre for endoscopic examination. Her trachea was intubated, while she was awake, with a 3.5-mm tracheal tube and spontaneous ventilation maintained with halothane and oxygen to avoid acute dilatation of the stomach, aspiration and inadvertent intubation of a tracheo-oesophageal fistula—the diagnosis with which the patient was referred. Laryngotracheobronchoscopy followed by oesophagoscopy confirmed the diagnosis of LTEC Type III. A central venous catheter was inserted for parenteral nutrition and the patient was transferred to the Paediatric Intensive Care Unit with the tracheal tube in place. CPAP was instituted.

After 2 weeks of parenteral nutrition and treatment for pneumonia, the patient returned to the operating theatre for total repair of the LTEC by a combined cervical and thoracic approach. It was considered essential to isolate the lungs so that ventilation could be controlled without danger of aspiration of gastric secretions or blood from the surgical procedure. A bifurcated endobronchial tube was constructed [9] as follows. The bevel of a 3.5-mm tracheal tube was cut off and the end of the tube split for 1 cm in the coronal plane. The distal 2.5-cm ends of two, 3.0-mm tracheal tubes were cut off and slid over the split ends of the 3.5-mm tracheal tube with the bevels facing laterally. This combination was stitched together at each joint with a No. 3-0 silk suture through the walls, but not the lumen, of the tubes. The endobronchial limbs were then cut along their lateral surfaces to permit ventilation of the upper lobes, and the endobronchial ends brought together by a slip-knot of No. 2 silk suture to facilitate passage of the bevelled ends through the glottis.

Anaesthesia was induced with halothane in oxygen through the existing, standard tracheal tube which

---

Riaz Ahmad, m.d., Khalid A. Sami, m.d. (Department of Anaesthesiology, MBC 22); Abdullah Rabeeah, m.d., f.r.c.s.(c.) (Department of Surgery); King Faisal Specialist Hospital and Research Centre, P.O. Box 3354, Riyadh 11211, Saudi Arabia.
Accepted for Publication: January 21, 1993.
Correspondence to R.A.

was then removed and the endobronchial tube passed gently through the vocal cords with the distal ends of the tube in an antero-posterior alignment. After passage through the cords, the tube was turned 90 ° and advanced until resistance was met. Auscultation of the lungs revealed good bilateral breath sounds and a chest x-ray showed the distal ends of the tube positioned at the carina. Assisted hand ventilation revealed no major air leak through the cleft and neuromuscular block was produced with atracurium. Radial arterial and central venous catheters were inserted. The patient was placed in the left lateral position and a right thoracotomy performed through the 3rd intercostal space. The LTEC was identified and dissected free. When the cleft was opened, the surgeon advanced the two wings of the endobronchial tube into the mainstem bronchi under direct vision. The cleft did not have sufficient tissue for reconstruction of both trachea and oesophagus. The distal oesophagus was dissected from the cleft and suture-ligated 3 cm proximal to the gastro-oesophageal junction. The trachea was repaired using the posterior oesophageal wall. The chest was closed and the proximal LTEC was repaired through a left cervical approach. A cervical oesophagostomy was created and a gastrostomy feeding tube was inserted.

Vital signs and oxygenation remained satisfactory throughout the procedure. The smallest oxygen saturation recorded by pulse oximetry was in the range 86–89 %. $P\text{CO}_2$ was 5–6 kPa. The patient was transferred to the Paediatric ICU with the endobronchial tube still in position and the lungs ventilated artificially. A suction catheter could be passed easily through the endobronchial tubes to each lung.

After 1 week of mechanical ventilation, the tracheal tube was found to have slipped back from its endobronchial position into the trachea and it was decided to replace the double-lumen tube with a conventional tracheal tube. During the process of extubation, one of the endobronchial wings became detached and remained in the trachea. The tube was removed easily with the help of a paediatric bronchoscope. The trachea was then reintubated with a 4.0-mm tracheal tube. Two weeks after repair, the trachea was extubated, but the patient soon developed respiratory distress. Bronchoscopy under general anaesthesia revealed tracheomalacia and tracheotomy was performed using a Shiley tracheostomy tube.

Six months after the surgery, the infant was brought back to the operating theatre, gastric tube interposition was used to replace the oesophageal gap, and the cervical oesophagostomy was closed.

DISCUSSION

Successful initial management of patients with Type III LTEC is based on early diagnosis, with precise definition of the extent of the cleft determined at endoscopy, establishment of a secure airway to provide protection against aspiration and adequate nutrition [4]. Early diagnosis requires a high index of suspicion, accurate interpretation of a barium oesophogram and thorough endoscopic evaluation [2]. Symptoms in the neonate range from inspiratory stridor, hoarse cry, cyanosis and feeding difficulties, to massive aspiration seen in Types III and IV [1, 2]. Diagnosis may often be delayed and there are case reports describing previous endoscopies [5], laryngoscopies by experienced anaesthetists [1] and even surgical repairs of tracheo-oesophageal fistula in which the presence of LTEC was not recognized [1, 2]. It is recommended that all infants thought to have tracheo-oesophageal fistula should undergo thorough endoscopy, as 6 % of tracheo-oesophageal fistula patients are found to have LTEC [1]. Endoscopic manoeuvres which increase the visibility of LTEC include placement of tracheal tube to stent the cleft open or pressure on the posterior larynx [5, 9]. Radiological examination with barium may fail to distinguish between communication and aspiration but, in experienced hands, opacification of the bronchial tree may be produced with less than 1 ml of contrast [9]. Early treatment of LTEC is essential to prevent the development of chronic lung disease [4].

Perioperative airway protection against aspiration in Type II clefts may be provided by placement of a conventional tracheal tube or tracheostomy below the inferior border of the cleft. Posterior migration of these breathing tubes into the oesophagus occurs with a more extensive LTEC, with potentially serious consequences [11]. High gastric division with gastrotomy drainage from the upper portion (to reduce the chances of aspiration) and gastrotomy feeding to the lower portion (for nutritional support) have been used in the perioperative management of LTEC patients [11]. Recent surgical literature, however, recommends a one-stage repair of LTEC with fundoplication [1].

In our opinion, anaesthesia for endoscopic evaluation of these patients should be managed with spontaneous ventilation and inhalation agents combined with topical anaesthesia of the upper airway [6, 7]. This technique reduces the potential for gastric distension and aspiration. Some Type I LTEC may be closed surgically at endoscopy [1]. Surgical repair of Type II clefts may be accomplished by one of several surgical approaches through the neck and requires anaesthesia via a tracheal tube or a tracheostomy, with care taken to ensure that the tip of the tube cannot slip into the oesophagus during surgical manipulation. With more extensive clefts, however, the airway must be secured by other methods. In one approach, for a cleft which was described as extending to the carina, a Foley catheter was passed into the stomach, the balloon inflated and subsequent traction applied [8]. The patient was then anaesthetized and the trachea intubated orally for a gastric division procedure. Two months later, the cleft was repaired through the neck and a tourniquet was placed around the distal trachea and oesophagus to prevent anaesthesia gas leakage or aspiration of blood and secretions. This technique was not considered suitable for a combined cervical and thoracic operation. It may be possible also to manage the airway during an extensive cleft repair with endobronchial intubation and one-lung anaesthesia using a conventional tracheal tube [10], although when the standard tube is withdrawn into the trachea at the completion of the repair, the tracheal suture line may be jeopardized by motion of the tube and during suctioning.

We chose to use the technique described by Donahoe and Gee [9]. We were unable to obtain the manufactured tube they described, but were able to fashion a similar "home made" version. This assembly allowed us complete control of the airway during thoracotomy and in the postoperative period. The movement of the endobronchial tube back into the trachea on the 8th day after operation was unfortunate, as we had planned to leave it for 2 weeks to give some time for healing to occur. The subsequent separation of the endobronchial wing was an unexpected and potentially dangerous complication. As a bifurcated tube is no longer commercially available as a special order product, cyclohexanone (Fisher Scientific catalogue), a PVC cement, can be used safely to make a stronger bond between the component parts [D. Flynn, Mallinckrodt Corp., personal communication].

Postoperative complications of LTEC repair include anastomotic leak, recurrence of the cleft or tracheo-oesophageal fistula, recurrent laryngeal nerve injury and persistent aspiration [1, 2]. After operation, the tracheal tube should remain *in situ* for several weeks until the suture lines have healed [4]. Long term tracheostomy is often needed because of tracheomalacia [4]. Fundoplication is advised to avoid the chronic aspiration which results from the long-term abnormality of swallowing function in patients with extensive LTEC despite restoration of the anatomical integrity of the trachea and oesophagus [1, 11].

REFERENCES

1. Du Bois JJ, Porkorny WJ, Harberg FJ, Smith RJH. Current management of laryngeal and laryngotrachealesophageal clefts. *Journal of Pediatric Surgery* 1990; **25**: 855–860.
2. Robie DK, Pearl RH, Gonsales C, Restuccia RD, Hoffman MA. Operative strategy for recurrent laryngeal cleft: a case report and review of the literature. *Journal of Pediatric Surgery* 1991; **26**: 971–974.
3. Pettersen G. Laryngo-tracheo-esophageal cleft. *Zeitschrift für Kinderchirurgie* 1969; **7**: 43–49.
4. Ryan DP, Muehrecke DD, Doody DP, Kim SH, Donahoe PK. Laryngotracheoesophageal cleft (type IV): Management and repair of lesions beyond the carina. *Journal of Pediatric Surgery* 1991; **29**: 962–970.
5. Armitage EN. Laryngotracheo-esophageal cleft—a report of three cases. *Anaesthesia* 1984; **39**: 706–713.
6. Yamashita M, Chinyanga HM, Steward DJ. Posterior laryngeal cleft—anaesthetic experiences. *Canadian Anaesthetists Society Journal* 1979; **26**: 502–505.
7. Kingston HGG, Harrison MW, Smith JD. Laryngotracheoesophageal cleft—a problem of airway management. *Anesthesia and Analgesia* 1983; **62**: 1041–1043.
8. Ruder CB, Glasler LC. Anesthetic management of laryngotracheoesophageal cleft. *Anesthesiology* 1977; **47**: 65–67.
9. Donahoe PK, Gee PE. Complete laryngotracheoesophageal cleft: management and repair. *Journal of Pediatric Surgery* 1984; **19**: 143–148.
10. Kubota H, Kubota Y, Toyodo Y, Ishida H, Asada A, Matsuuva H. Selective blind endobronchial intubation in children and adults. *Anesthesiology* 1987; **67**: 587–589.
11. Cotton RT, Schreiber JT. Managemente of laryngotracheoesophageal cleft. *Annals of Otology, Rhinology and Laryngology* 1981; **90**: 401–405.

British Journal of Anaesthesia 1993; **70**: 699–707

CORRESPONDENCE

HAEMOSTASIS AND THROMBELASTOGRAPHY: A CAUTIOUS NOTE

Sir,—We read with interest the recent review article entitled "Thrombelastography" by Mallett and Cox [1]. In the article, the authors attempted to examine the growing controversy on the clinical use of thrombelastography (TEG) in cardiac surgery and other operative procedures. The review article reflected that TEG may predict postoperative blood loss [2], yet failed to discuss the observations made by Wang and colleagues [3] and Horkay and colleagues [4] which identified no predictive power of an abnormal TEG profile for excessive postoperative haemorrhage in adult cardiothoracic surgical patients. Paradoxically, both groups identified TEG evidence of a hypercoagulable state in several patients after surgery (Wang and colleagues 13%, Horkay and colleagues 60%)—findings inconsistent with previously reported haemorrhage-induced TEG derangements. However, in contrast, in other studies performed in this unit, in a cohort of paediatric patients undergoing open heart surgery, TEG predicted with 100% accuracy (specificity 73%) those patients who developed excessive bleeding [5]. This was reflected by a TEG *hypocoagulable state* (diminished maximum amplitude (MA) phase $P < 0.01$, prolonged clot formation time (K phase) $P < 0.05$). The reviewers also cited the work of Tuman and colleagues [6], who reported that massive blood loss was associated with a trend towards increased coagulability (where losses were replaced only with crystalloid and packed red blood cells) which is at variance with the premise of the proposed potential of TEG to predict bleeding.

Furthermore, Mallett and Cox suggested that TEG may be a useful means of assessing *in vitro* platelet function in whole blood, citing an abstract which identified correlations of the MA phase of TEG with platelet count and also with aggregation responses to collagen and ADP [6]. However, at variance with this finding, later in the review they cited data from several groups [7–9] demonstrating the inability of TEG to delineate platelet dysfunction in the presence of small doses of aspirin, a known inhibitor of platelet aggregation. They explain this observation by reference to the inability of aspirin to inhibit thrombin-stimulated aggregation. Yet one would expect thrombin to have been present similarly as a confounding factor in the study identifying the aggregation correlates of TEG [6].

In conclusion, we recommend that caution be exercised when interpreting TEG in different patient populations (e.g. adults and paediatric) and settings when treating haemostatic derangements. Prospective longitudinal studies are required to assess the accuracy and specificity of TEG prediction of operative bleeding and more powerful interventional studies are required to determine if TEG-guided blood product administration can reduce transfusion requirements or blood loss.

N. K. Gupta
P. G. Martin
D. Greenstein
D. R. Walker
Killingbeck Hospital
Leeds

1. Mallett SV, Cox DJA. Thrombelastography. *British Journal of Anaesthesia* 1992; **69**: 307–313.
2. Spiess BD, Tuman KJ, McCarthy RJ, DeLaria GA, Schillo R, Ivankovich AD. Thrombelastography as an indicator of post-cardiopulmonary bypass coagulopathies. *Journal of Clinical Monitoring* 1987; **3**: 25–30.
3. Wang J-S, Lin C-Y, Hung W-T, O'Connor MF, Thisted RA, Lee BK, Karp RB, Yang M-W. Thrombelastogram fails to predict postoperative hemorrhage in cardiac patients. *Annals of Thoracic Surgery* 1992; **53**: 435–439.
4. Horkay F, Martin P, Gupta NK, Satur CMR, Walker DR. Transient hypercoagulability in adult patients following open-heart surgery. *Perfusion* 1992; **7**: 119–123.
5. Martin P, Horkay F, Rajah SM, Walker DR. Monitoring of coagulation status using thrombelastography during paediatric open heart surgery. *International Journal of Clinical Monitoring and Computing* 1991; **8**: 183–187.
6. Tuman KJ, McCarthy RJ, Patel RV, Ivankovich AD. Comparison of thrombelastography and platelet aggregometry. *Anesthesiology* 1991; **75**: A433.
7. De Gaetano G, Vermylen J. Effect of aspirin on the thrombelastograph of human blood. *Thrombosis et Diathesis Haemorrhagica* 1973; **30**: 494–498.
8. Mallett SV, Platt M. Role of thrombelastography in bleeding diatheses and regional anaesthesia. *Lancet* 1991; **338**: 765–766.
9. Orlikowski CEP, Moodley J, Rocke DA. Thrombelastography in pregnant patients on low dose aspirin. *Lancet* 1991; **338**: 1276–1277.

Sir,—Thank you for the opportunity to reply to the letter by Gupta and associates.

The recent papers to which they refer [1, 2] were published after our review was submitted and therefore could not be considered at that time.

These papers appear to contradict previously published studies on this subject [3–5] in that they were unable to demonstrate that thrombelastography (TEG) can reliably predict postoperative bleeding in cardiac surgical patients. However, differences in these studies should be interpreted with care. Whether the patient populations are strictly comparable is debatable, given the extremely high prevalence of fibrinolysis and hypocoagulation before operation [1]. Also, where there is an unusually high prevalence of preoperative coagulopathies it is important to correlate TEG abnormalities with other coagulation tests in order to differentiate adequately real coagulation problems from any artefact of the tracings which could introduce methodological flaws and problems with interpretation of the data. It is difficult also to make direct comparisons when there are obvious differences in the design and construction of these studies.

Postoperative haemorrhage is related to many interrelated factors, including the quality of surgical haemostasis, the nature of the haemostatic defects, patient temperature, neuroendocrine responses and drug therapy; comparisons of results must take these factors into consideration. An abnormal TEG *per se* does not necessarily imply that particular patients may bleed excessively; however, if they do, it offers some objective variables on which to base corrective therapy. It is also of note that *all* reported series, including those of Wang and colleagues [1] and Horkay and colleagues [2], confirm the specificity of the TEG in detecting surgical bleeding in cardiac surgical patients.

The study by Tuman and colleagues [6], on the effects of progressive (normovolaemic) surgical blood loss on the TEG, demonstrated that *normal* individuals have a "coagulation reserve" and can have adequate haemostatic function despite dilution of their clotting factors and platelet numbers. This is compatible with the fact that a 20% factor value is sufficient to maintain haemostasis. It is only when dilution becomes excessive (> 80% of estimated blood volume) that a proportion of patients develop clinical and TEG evidence of hypocoagulability. This illustrates how important it is that treatment is given on an individual basis, rather than according to a generalized format, and that coagulation is monitored serially during major procedures.

Postoperative hypercoagulability is well known to occur as part of the stress response to surgery and trauma, and is a particularly common finding in patients with cardiovascular disease [7]. It is not surprising, therefore, that both Wang's and Horkay's groups [1, 2] found a significant incidence after surgery. Identification by the TEG of a hypercoagulable state is of obvious clinical importance because of the association with a high incidence of postoperative thrombotic events [8].

All published studies to date show that low-dose aspirin does not alter the TEG and therefore it cannot be used to identify those patients at increased risk of bleeding. The mechanisms by which aspirin acts *in vivo* to protect against thrombotic complications are still incompletely understood. Aspirin irreversibly inactivates cyclo-oxygenase and blocks the arachidonic acid pathway to the platelet release reaction [9]. ADP and collagen are potent agonists that stimulate platelet aggregation *independently* of the arachidonic acid pathway [10] and therefore the MA is not affected by aspirin. The TEG is unable to measure the initial phase of platelet adhesion which requires interaction with the vascular endothelium. The TEG monitors the thrombin generation of a blood sample. Aspirin does not significantly affect thrombin generation, therefore the structural function of platelets in a thrombin-induced clot is still measurable in the TEG and any aspirin effects may not be observable for the onset of clotting. Measurement of the bleeding time still remains the most reliable simple test of aspirin effect on platelet function [11].

The successful implementation of TEG as a tool for monitoring coagulation requires care and experience in performing the test and also in interpreting its results. Despite its limitations, it helps to improve the assessment of coagulation status during operation. It would seem logical that a method of monitoring coagulation that allows serial measurement of whole blood clot formation and stability is of more clinical relevance to a patient undergoing surgery than a limited series of tests that are performed on citrated plasma and look only at the early stages of clot formation. As with any form of monitoring, decisions regarding therapeutic intervention should always be based on *clinical* grounds in addition to the results of tests.

S. V. MALLETT
D. J. A. COX
Royal Free Hospital
London

1. Wang JS, Lin CY, Hung WT, O'Connor MF, Thisted RA, Lee BK, Karp RB, Yang MW. Thrombelastography fails to predict postoperative hemorrhage in cardiac patients. *Annals of Thoracic Surgery* 1992; 53: 435–439.
2. Horkay F, Martin P, Gupta NK, Stur CMR, Walker DR. Transient hypercoagulability in adult cardiac patients following open heart surgery. *Perfusion* 1992; 7: 119–123.
3. Tuman KJ, Speiss BD, McCarthy RJ, Ivankovich AD. Comparison of viscoelastic measures of coagulation after cardiopulmonary bypass. *Anesthesia and Analgesia* 1989; **69**: 69–75.
4. Spiess BD, Tuman KJ, McCarthy RJ, DeLaria GA, Schillo R, Ivankovich AD. Thromboelastography as an indicator of post cardiopulmonary bypass coagulopathies. *Journal of Clinical Monitoring* 1987; 3: 25–30.
5. Martin P, Horkay F, Rajah SM, Walker DR. Monitoring of coagulation status using thromboelastography during paediatric open heart surgery. *International Journal of Clinical Monitoring and Computing* 1991; **8**: 183–187.
6. Tuman KJ, Spiess BD, McCarthy RJ, Ivankovich AD. Effects of progressive blood loss on coagulation as measured by thromboelastography. *Anesthesia and Analgesia* 1987; **66**: 857–863.
7. Gibbs NM, Crawford PM, Michalopoulos N. Postoperative changes in coagulant and anticoagulant factors following abdominal aortic surgery. *Journal of Cardiothoracic and Vascular Anesthesia* 1992; **6**: 680–685.
8. Tuman KJ, McCarthy RJ, March RJ, DeLaria GA, Patel RV, Ivankovich AD. Effects of epidural anesthesia and analgesia on coagulation and outcome after major vascular surgery. *Anaesthesia and Analgesia* 1991; 73: 696–704.
9. George JN, Shattil SJ. The clinical importance of acquired abnormalities of platelet function. *New England Journal of Medicine* 1991; 324: 27–39.
10. Coller BS. Platelets and thrombolitic therapy. *New England Journal of Medicine* 1990; 332: 33–42.
11. Trentalange MJ, Walts LF. A comparison of thromboelastogram and template bleeding time in the evaluation of platelet function after aspirin ingestion. *Journal of Clinical Anesthesia* 1991; 5: 377–381.

CONTINUOUS SUBARACHNOID INFUSION OF 0.125% BUPIVACAINE FOR ANALGESIA DURING LABOUR

Sir,—The findings of McHale and colleagues [1] raise several points for discussion. The authors claim that the subarachnoid administration of dilute solutions of bupivacaine produces effective analgesia in labour. However, on further examination there appear to be few advantages of this technique compared with extradural infusions. Moreover, the disadvantages associated with this method should not be overlooked.

This method of analgesia is associated with a high degree of motor block which may have accounted for the increased rate of instrumental delivery, as relaxation of the muscles of the pelvic floor may lead to malrotation of the fetal presenting part [2]. The aetiology of long-term backache after childbirth has been linked with motor block during labour [3]. Those authors stated that "the mother was allowed to adopt any position she found comfortable." Labouring women and their attending midwives must be taught the correct position to be adopt after the administration of regional analgesia: mothers must ensure that the back is kept straight, minimizing stressful postures and therefore reducing long-term backache. Maternal satisfaction has been demonstrated to be greater when motor block has been minimized by the use of spinal opioids [4]; although mothers in McHale and colleagues' study considered that analgesia had been excellent or good when questioned following delivery, there was no such control group with which a comparison could be made.

Long-term neurological damage after subarachnoid infusions [5] was not discussed in the paper by McHale and colleagues. Although this complication has been reported only after the use of stronger concentrations of local anaesthetics, the seriousness of this problem warrants its inclusion.

Motor block was said, by the authors, to be undertaken on the basis of the Bromage motor scale. However, the scale described bears little resemblance to Bromage's original scale [6] and although many subsequent authors have modified this scale [7], the method used by McHale and colleagues lacked accuracy, as it assessed the whole leg rather than the hip, knee and ankle joints as intended by Bromage.

The authors suggest that one of the benefits of their technique would be rapid extension of the block in the event of an operative or instrumental delivery. They describe how, with 0.5% heavy bupivacaine 1–2 ml, the upper limit of the block produced a sensory loss to T4 in less than 13 min. A recent study by Price and colleagues [8] demonstrated that extradural block could be extended for Caesarean section with 2% lignocaine in less time than this.

The quality of analgesia produced by the subarachnoid infusions is described by the authors as effective. However, when one considers that the mean duration of labour was 3 h 13 min and the average number of top-ups was 2.8, it appears that this method is far from effective. With an infusion technique, even using local anaesthetics as the sole agent, this number of top-ups is unacceptably large. A review by Gaylard [9] cited many extradural infusion procedures in which the number of top-ups required was much smaller.

With the very high instrumental delivery rate reported, the authors comment that "this may be a reflection of the effectiveness of the analgesia in the second stage." The maintenance of infusion analgesia throughout the second stage has been demonstrated by Chestnut and colleagues [10] not to increase the number of instrumental deliveries. We have achieved a 60% spontaneous delivery rate in our extradural population using an infusion of 0.08% bupivacaine containing sufentanil $2\ \mu g\ ml^{-1}$. Infusions were continued into the second stage and nearly all women reported minimal or no discomfort at delivery [11].

Overall, the technique described in the paper has little to commend it, and many potential disadvantages such as excessive motor block, a high incidence of instrumental and operative deliveries, inadequate maintenance of analgesia and the potential for neurological sequelae.

R. RUSSELL
St Thomas' Hospital
London

1. McHale S, Mitchell V, Howsam S, Carli F. Continuous subarachnoid infusion of 0.125% bupivacaine for analgesia during labour. *British Journal of Anaesthesia* 1992; **69**: 634–636.
2. Walton P, Reynolds F. Epidural analgesia and instrumental deliveries. *Anaesthesia* 1984; 39: 218–223.
3. MacArthur C, Lewis M, Knox EG, Crawford JS. Epidural anaesthesia and long term backache after childbirth. *British Medical Journal* 1990; **301**: 9–12.

4. Murphy JD, Hutchinson K, Bowden MI, Lewis M, Cooper GM. Bupivacaine versus bupivacaine plus fentanyl for epidural analgesia: effect on maternal satisfaction. *British Medical Journal* 1991; **302**: 564–567.
5. Rigler ML, Drasner K, Krejcie TC, Yelich SJ, Scholnick FT, DeFontes J, Bohner D. Cauda Equina Syndrome after continuous spinal anesthesia. *Anesthesia and Analgesia* 1991; **72**: 275–281.
6. Bromage PR. A comparison of the hydrochloride and carbon dioxide salts of lidocaine and prilocaine in epidural analgesia. *Acta Anaesthesiologica Scandinavica* 1965; **16**: S55–69.
7. Russell R. Assessment of motor blockade during epidural analgesia in labour. *International Journal of Obstetric Anesthesia* 1992; **1**: 230–234.
8. Price ML, Reynolds F, Morgan BM. Extending epidural blockade for emergency caesarean section: evaluation of 2% lignocaine with adrenaline. *International Journal of Obstetric Anesthesia* 1992; **1**: 13–18.
9. Gaylard D. Epidural analgesia by continuous infusion. In: Reynolds F, ed. *Epidural and Spinal Blockade in Obstetrics*. London: Baillière-Tindall, 1990; 49–58.
10. Chestnut DH, Bates JN, Choi WW. Continuous infusion epidural analgesia with lidocaine. Efficacy and influence during the second stage of labour. *Obstetrics and Gynecology* 1987; **69**: 774–780.
11. Russell R, Groves P, Reynolds F. Is opioid loading necessary before opioid/local anaesthetic epidural infusions? A randomized double-blind study in labour. *International Journal of Obstetric Anesthesia* 1993; (in press).

Sir,—Thank you for the opportunity to reply to Dr Russell's comments. We did not advocate the use of continuous subarachnoid infusions of local anaesthetic for analgesia instead of extradurals, but merely reported our findings when using a technique which had not been used before during labour.

The implication that the instrumental delivery rate in our group of primiparae (40%) receiving regional analgesia during labour is exceptionally high is unfounded. Others have reported rates greater than 40% [1–3]. Kaminski, Stafl and Aiman compared a group of primiparae receiving extradural analgesia with a control group. The frequency of instrumental delivery was 52% in the extradural group, compared with 23% in the controls [4]. The rotational forceps rate of 15% in our study is similarly unexceptional, as other groups have reported midcavity forceps delivery rates of 12% in primiparae receiving extradural analgesia [4]. This suggests that pelvic muscle relaxation after intrathecal infusions did not lead to malrotation of the fetal presenting part.

The aetiology of long-term backache after labour is not yet known, and as yet there are no prospective studies linking the degree of motor block to the incidence of long-term backache [5].

Our assessment of motor block was indeed on a four-point scale as described by Bromage [6]. Full flexion of both knees and feet implied absence of motor block; that the mother was just able to move her knees indicated partial motor block; no knee movement but still foot movement implied almost complete block; inability of the mother to move either feet or knees indicated complete motor block.

Only four women required extension of the subarachnoid block for Caesarean section. Although one block took 13 min to reach T4, the other blocks were established in 5, 6 and 10 min. Whereas the appropriate drug and volume for an extradural top-up are known, we were naturally cautious when we administered bupivacaine into the subarachnoid space. As experience with this technique increases it will become more refined and, similarly, as different infusion rates are used throughout labour the number of top-ups required to maintain analgesia will decrease.

All new techniques are associated with a learning curve. The advantages of a rapid onset of good analgesia, with the potential for manipulation of the solution injected and ease of extension of the block in the case of an operative or instrumental delivery, suggest that there may be a place for subarachnoid infusions during labour. However, further use of the technique will be limited as a result of the cases of cauda equina syndrome in America. These have led to the Food and Drug Administration recalling all licences for intrathecal use of microcatheters. In these cases the drugs involved were 5% lignocaine with 7.5% glucose (three cases) and 1% amethocaine with 10% glucose (one case). The aetiology of the neural damage has been postulated to result from a combination of maldistribution and a relatively large dose of local anaesthetic around the nerve roots [7].

S. McHale
F. Carli
Northwick Park Hospital
Harrow

1. Crawford JS. Lumbar epidural block in labour: a clinical analysis. *British Journal of Anaesthesia* 1972; **44**: 66.
2. Morgan BM, Rehor S, Lewis PJ. Epidural analgesia for uneventful labour. *Anaesthesia* 1980; **35**: 57.
3. Walton P, Reynolds F. Epidural analgesia and instrumental delivery. *Anaesthesia* 1984; **39**: 218.
4. Kaminski HM, Stafl A, Aiman J. The effect of epidural analgesia on the frequency of instrumental obstetric delivery. *Obstetrics and Gynecology* 1987; **69**: 770–773.
5. Russell R. Assessment of motor blockade during epidural analgesia in labour. *International Journal of Obstetric Anesthesia* 1992; **4**: 230–234.
6. Bromage PR. A comparison of the hydrochloride and carbon dioxide salts of lidocaine and prilocaine in epidural analgesia. *Acta Anaesthesiologica Scandinavica* 1965; **16**: S55–69.
7. Rigler ML, Drasner K, Krejcie TC, Yelich J, Scholnick FT, Defontes J, Bohner D. Cauda equina syndrome after continuous spinal anesthesia. *Anesthesia and Analgesia* 1991; **72**: 275–281.

PREOPERATIVE DRINKING AND GASTRIC CONTENTS

Sir,—We share Professor Strunin's puzzlement [1] that there is an implication of something revolutionary in the paper of Drs Phillips, Hutchinson and Davidson [2] on preoperative fasting. In July of 1991, we published a paper [3] which investigated virtually the same regimen and drew exactly the same conclusion. Of particular note is the similarity of the confidence intervals of the difference in the residual gastric volumes of the two groups in each paper. This was present despite smaller sized study groups.

Among the minor differences between this new study and ours are the following: we allowed only water whereas they allowed "clear fluids"; they used a double-lumen tube to empty the stomach: we used a single-lumen tube and rolled the patient during aspiration; *all* our patients were premedicated with temazepam; the mean gastric pH of both our groups were less than 2.5 (in both studies the confidence intervals of differences in gastric pH are wide).

M. S. Read
R. S. Vaughan
University Hospital of Wales
Cardiff

1. Strunin L. How long should patients fast before surgery? Time for new guidelines. *British Journal of Anaesthesia* 1993; **70**: 1–3.
2. Phillips S, Hutchinson S, Davidson T. Preoperative drinking does not affect gastric contents. *British Journal of Anaesthesia* 1993; **70**: 6–9.
3. Read MS, Vaughan RS. Allowing pre-operative patients to drink. Effects on patients' safety and comfort of unlimited oral water until two hours before anaesthesia. *Acta Anaesthesiologica Scandinavica* 1991; **35**: 591.

Sir,—In his Editorial on fasting before surgery [1], Professor Strunin questions why none of Mendelson's patients [2] died after inhaling liquid acid gastric contents, yet aspiration is a significant cause of maternal mortality today. We wish to offer an explanation. As stated in Mendelson's paper, a mixture of nitrous oxide, oxygen and ether was used in all cases. As late as 1959, junior anaesthetists in one London teaching hospital were forbidden to use any other technique for all forceps deliveries. Despite atropine 0.6 mg, maternal salivation was invariably profuse. Coughing, swallowing, retching and vomiting were considered normal events at induction. Partial alkalinization of gastric contents by saliva, in-addition to a diluent and "lining" effect of copious tracheobronchial secretions, might have made aspiration a survivable insult. The contemporary practice of i.v. agent and suxamethonium in rapid sequence does not afford the lungs this potential protection.

D. M. LEVY
University of Sheffield Medical School
Sheffield
M. E. TUNSTALL
University of Aberdeen
Aberdeen

1. Strunin L. How long should patients fast before surgery? Time for new guidelines. *British Journal of Anaesthesia* 1993; 70: 1–3.
2. Mendelson CL. The aspiration of stomach contents into the lungs during obstetric anesthesia. *American Journal of Obstetrics and Gynecology* 1946; 52: 191–205.

Sir,—I agree with Professor Strunin [1] that it is time for new guidelines on preoperative starvation. I wish to raise one issue and make one comment.

First, in the United States several children are admitted just before surgery and may recently have been or still be, chewing bubble gum! There are several approaches amongst anaesthesia staff: some ignore the chewing of gum and accept the children as starved; others take the view that chewing gum increases gastric secretion via conditioned and unconditioned reflexes, such as sight, smell and taste, leading to increased gastric volume, at low pH, which requires a 6-h postponement [2]; yet others believe that chewing gum is equivalent to a clear liquid challenge and should be cleared from the stomach within a 3-h postponement; a fourth group argue that the child who drank recent clear fluids will have diluted his gastric contents and will thus be at less risk than the child who has only chewed gum. This last group would recommend offering a clear liquid drink and postponing for 3 h. Until recently, I followed the first option, but I am now considering adopting the last approach. A small postponement would be less disruptive to the theatre list, but may also discourage the child from chewing gum before any subsequent surgery.

Second, in healthy patients presenting for elective surgery it is perfectly acceptable to allow a 6-h starvation period for solid foods and 3 h for clear liquids. However, despite this apparent simplicity, I have still found patient, nurse and surgical confusion in trying to implement such instructions. The "double time limits" adds to errors, and to the number of rules broken. There have also been several episodes of misunderstanding associated with the term "clear" liquid. Patients have interpreted this to mean "pure", and have allowed themselves assortments of puréed fruit, such as apple. This concept must be made clear to patients or perhaps, as a compromise, patients might only be allowed to drink once in hospital and under nursing vigilance.

If in doubt, a conservative approach is the safest.

C. MATHER
Children's Hospital and Medical Center
Seattle

1. Strunin L. How long should patients starve before surgery? Time for new guidelines. *British Journal Anaesthesia* 1993; 70: 1–3.
2. Kradel B, Hackett A, Johnstone R. NPO includes chewing gum. *Anesthesia and Analgesia* 1992; 74: 621.

Sir,—Drs Read and Vaughan gently chide me for having missed their paper [1] in my editorial [2]. It is, however, nice to see that their results regarding preoperative fasting in Wales are similar to those observed in England and North America. This statement should not be construed as facetious or unkind. Among the many objections that the Medical Ethics sub-Committee of the University of Calgary raised to the procedures of the Canadian studies referenced in my editorial [2] was their belief that results obtained in other countries relating to gastric emptying [3] could not be assumed to be the same as may be obtained in Canada. Studies such as those of Read and Vaughan have proved the Ethics Committee wrong. One criticism that can be levelled at Drs Read and Vaughan is that, having shown that allowing preoperative patients unlimited oral water until 2 h before anaesthesia was not hazardous, they made no recommendations with regard to changing current practice. Others have taken this step and have drawn up guidelines with regard to what is meant by "clear fluids" [4–6] and have not found that patients have difficulties in distinguishing between solids and liquids. It seems that water, carbonated drinks, non-particulate fruit juices and modest quantities of milk or sugar in tea or coffee are all acceptable within the definition of "clear fluids".

The description of ether anaesthesia by Drs Levy and Tunstall may be relevant in relationship to Mendelson's observation [7] that none of his patients died after fluid aspiration. However, ether anaesthesia need not be quite so unpleasant and yet may be safe for obstetrics even by open drop [8]. I still hold the view [graphically described in the *Report on Confidential Enquiries Into Maternal Deaths in England and Wales*, 1976–1978, pp. 80–81] that, although pulmonary aspiration of gastric contents may be the starting point for a potential maternal death, it is other factors such as repeated attempts at tracheal intubation accompanied by intermittent positive pressure ventilation without a secure airway and the resultant hypoxia, inadequate equipment and inexperienced personnel that combine to make death a certainty.

With regard to children, or adults for that matter, chewing gum, I know of no study which equates this with eating and therefore these patients may be managed in the same way as any other starved individual. However, as the letter [9] by Kradel, Hackett and Johnstone describes suctioning gum from the stomach after tracheal intubation, there may be some hazard if patients are anaesthetized still chewing their gum. Therefore, bearing in mind the old Lonnie Donegan song "*Does your chewing gum lose its flavour on the bedpost over-night?*", perhaps the preoperative check list should include making sure that patients have deposited their gum in an environmentally friendly place before induction of anaesthesia.

L. STRUNIN
Editor of Educational Reviews

1. Read MS, Vaughan RS. Allowing pre-operative patients to drink: effects on patients' safety and comfort of unlimited oral water until 2 hours before anaesthesia. *Acta Anaesthesiologica Scandinavica* 1991; 35: 591–595.
2. Strunin L. How long should patients fast before surgery? Time for new guidelines. *British Journal of Anaesthesia* 1993; 70: 1–3.
3. Hunt JN. Some properties of an alimentary osmoreceptor mechanism. *Journal of Physiology (London)* 1956; 132: 267–288.
4. Maltby JR, Strunin L. Nil by mouth after midnight. *Anaesthesia* 1992; 47: 1108–1109.
5. Matthews AJ, Coultas RJ. Nil by mouth after midnight. *Anaesthesia* 1992; 47: 1109.
6. Armstrong R. Nil by mouth after midnight. *Anaesthesia* 1992; 47: 1109.
7. Mendelson CL. The aspiration of stomach contents into the lungs during obstetric anesthesia. *American Journal of Obstetrics and Gynecology* 1946; 52: 191–205.
8. Maltby JR, Malla DS, Dangol H. Open drop ether anaesthesia for Caesarean section: A review of 420 cases in Nepal. *Canadian Anaesthetists Society Journal* 1986; 33: 651–655.
9. Kradel B, Hackett A, Johnstone R. NPO includes chewing gum. *Anesthesia and Analgesia* 1992; 74: 621.

Sir,—Thank you for the opportunity to respond to Drs Read and Vaughan. As they (and the Editorial accompanying our article) have pointed out, there is nothing revolutionary about suggesting that the period of fluid fasting before surgery should be reduced.

What is surprising is that the majority of anaesthetists still expect and teach that a 4–6 h fast is necessary before elective surgery. In practice, this period is often much longer; in our study the mean fasting time exceeded 12 h [1]. Indeed, the increasing body of research into this subject continues to find that the current guidelines are excessive [2–4].

Sceptics should gain reassurance from the fact that, despite variations in study design, including those noted by Drs Read and Vaughan, similar conclusions have been reached in all these reports. This is most unlikely to be a result of chance or flawed study design.

Our study merely brings to the attention of the profession a long-accepted practice which adds significant discomfort for the majority of elective surgical patients in return for no increase in safety.

S. Phillips
Hospital for Sick Children
London
S. Hutchinson
St Helier Hospital
Carshalton
T. Davidson
The Royal Marsden Hospital
London

1. Phillips S, Hutchinson S, Davidson T. Preoperative drinking does not affect gastric contents. *British Journal of Anaesthesia* 1993; **70**: 6–9.
2. Read MS, Vaughan RS. Allowing preoperative patients to drink. Effects on patient's safety and comfort of unlimited oral water until two hours before anaesthesia. *Acta Anaesthesiologica Scandinavica* 1991; **35**: 591–595.
3. Agarwal A, Chari P, Singh H. Fluid deprivation before operation. The effect of a small drink. *Anaesthesia* 1989; **44**: 632–634.
4. Maltby JRT, Lewis P, Martin A, Sutherland LR. Gastric fluid and pH in elective patients following unrestricted oral fluid until 3 hours before surgery. *Canadian Journal of Anaesthesia* 1991; **38**: 425–429.

EXTRADURAL ABSCESS IN THE POSTPARTUM PERIOD

Sir,—We read with interest the case report by Dr Ngan Kee and colleagues [1] who described a patient in whom an extradural abscess developed after insertion of an extradural catheter for postoperative pain relief after Caesarean section. We report a case of an extradural an extradural abscess which developed spontaneously in a postpartum patient.

A 31-yr-old woman was referred to the regional neurosurgical unit with a 4-day history of severe mid-thoracic back pain, difficulty in micturition, and spastic leg weakness. Eight weeks previously she had been delivered of her fourth child. She did not receive extradural analgesia, and there were no untoward obstetric events. On examination she had marked loss of power in both legs and was unable to stand. Lower limb reflexes were pathologically brisk with upgoing plantars. She had loss of sensation to light touch below T10. Myelography confirmed the presence of a blocked flow of contrast at T8–9. She underwent urgent thoracic laminectomy and drainage of an abscess at T8–9. The fluid aspirated subsequently grew *Staphylococcus aureus* sensitive to benzylpenicillin. Further investigations after operation (including abdominal and pelvic ultrasound) revealed no obvious source for the infection. Six weeks after surgery, neurological deficit was limited to leg weakness on exertion.

This case demonstrates that, although an extradural catheter may provide a nidus for the formation of an extradural abscess, a causal relationship cannot necessarily be assumed. The reported incidence of this complication after lumbar extradural analgesia in obstetrics is less than the rate of spontaneous spinal extradural abscess in the general hospital population. Dr Ngan Kee and colleagues point out that the incidence of spontaneous spinal extradural abscess is 0.2–1.2 per 10000 hospital admissions. The case report of Dr Ngan Kee and colleagues is only the second reported case associated with lumbar extradural catheterization in labour, and they quoted an incidence of 1 in 505000 obstetric extradural blocks, from a previous study [2]. Extradural abscess can develop spontaneously in the postpartum period, and similar neurological problems can occur after general anaesthesia [3].

A. J. Kitching
A. S. C. Rice
John Radcliffe Infirmary
Oxford

1. Ngan Kee WD, Jones MR, Thomas P, Worth RJ. Extradural abscess complicating extradural anaesthesia for Caesarean section. *British Journal of Anaesthesia* 1992; **69**: 647–652.
2. Scott DB, Hibbard BM. Serious non-fatal complications associated with extradural block in obstetric practice. *British Journal of Anaesthesia* 1900; **64**: 537–541.
3. Schreiner EJ, Lipson SF, Bromage PR, Camporesi EM. Neurological complications following general anaesthesia. Three cases of major paralysis. *Anaesthesia* 1983; **38**: 226–229.

Sir,—We read with interest the article by Ngan Kee and colleagues describing a rare complication of extradural anaesthesia, resulting in the patient making a complete recovery after back surgery to release the abscess [1]. *Staphylococcus aureus* was probably a skin contaminant in the case presented, with the bacteria seeding the extradural space by colonizing either down or around the catheter.

Aseptic technique is essential to prevent wound and catheter contamination with skin bacteria. In surgery, 1% iodine has been used as a skin disinfectant for many years and traditionally involves a 10-min scrub. Alexander, Aeri and Plettner described a 1-min preparation with 70% alcohol or 2% iodine in 90% alcohol that produced a reduction in bacterial skin flora similar to that obtained with the 10-min povidone-iodine (1% free iodine) skin preparation [2]. Multidose povidone-iodine bottles have been shown to grow a variety of organisms [3]. At the 1992 Society of Obstetric Anesthesia and Perinatology meeting, Birnbach and colleagues presented the results of a study in which cultures were obtained from povidone-iodine bottles from the labour suite. Bacterial swabs from the cap and solutions revealed *Staphylococcus haemolyticus* and *S. epidermidis*, which were in greater quantities in previously opened bottles compared with newly opened bottles.

In preparing the skin for extradural anaesthesia, we recommend that sterile povidone-iodine swabs should be used in a spiral motion with each swab stick starting from the point of intended needle insertion and working outwards to prevent cross contamination. Alcohol 70% should be used to rinse the iodine off, and for maximal effect, it is important to allow the alcohol to evaporate, rather than swabbing it dry.

The use of polyurethane dressings has been shown to increase the colonization of skin by bacteria, mostly because of accumulation of sweat, which acts as a medium for bacterial growth [4, 5]. Hoffman and colleagues carried out an extensive review and meta-analysis to estimate the effect of transparent polyurethane film on central venous catheter tip infections [6]. They concluded that there was a significantly increased incidence of catheter-tip related infections with the use of polyurethane dressings. Changing the dressings more frequently would decrease the incidence of infection, but would certainly add to the cost of site care. Although this work was performed on central and peripheral i.v. catheters, the principles of colonization of skin and catheter by bacteria are similar. Additionally, with the high ambient temperatures of delivery suites and neonatal areas, the mother is more prone to sweating under a polyurethane film. The collection of sweat and high temperatures in turn would lead to an increased rate of bacterial cell division and add to the risk of catheter-related infections. Therefore, we recommend that polyurethane dressings should not be used on extradural catheter sites, especially when the catheter is likely to be used for periods greater than 24 h.

G. M. S. Vasdev
C. H. Leicht
Mayo Clinic
Rochester, Minnesota

1. Ngan Kee WD, Jones MR, Thomas P, Worth RJ. Extradural abscess complicating extradural anaesthesia for Caesarean section. *British Journal of Anaesthesia* 1992; **69**: 647–652.
2. Alexander JW, Aeri S, Plettner JP. Development of a safe and effective one minute preoperative skin preparation. *Archives of Surgery* 1985; **120**: 1357–1361.
3. Craven DE, Moody B, Connolly MG, Kollisch NR, Stottmeier KD, McCabe WR. Pseudobacteremia caused by povidone-iodine solution contaminated with *Pseudomonas cepucia*. *New England Journal of Medicine* 1981; **305**: 621–623.
4. Maki D, Will L. Colonization and infection associated with transparent dressings for central venous catheters: a com-

parative trial. *Program and Abstracts of the Association for Practitioners in Infection Control Educational Conference*, 1984.

5. Craven DE, Lichtenberg DA, Kunches M. A randomized study comparing a transparent polyurethane dressing to a dry gauze dressing for peripheral intravenous catheter sites. *Infection Control* 1985; **6**: 361–366.
6. Hoffman KK, Weber DJ, Samsa GP, Rutala WA. Transparent polyurethane film as an intravenous catheter dressing. A meta-analysis of the infection risk. *Journal of the American Medical Association* 1992; **267**: 2072–2076.

Sir,—Drs Kitching and Rice describe an interesting case of puerperal extradural abscess after normal delivery without extradural analgesia. A similar case was described by Male and Martin [1], who reported an extradural abscess that developed 6 days after normal delivery in a 22-yr-old woman who also had not received extradural analgesia. This patient had been admitted 10 days before delivery suffering from infective hepatitis with hepatocellular dysfunction and jaundice, whereas the patient described by Drs Kitching and Rice was presumably healthy.

I agree that it is possible for an extradural abscess to occur after extradural catheterization without a causal relationship existing. However, I would emphasize several points. The incidence of spontaneous extradural abscess in the general hospital population is estimated at 0.2–1.2 per 10000 which, indeed, is greater than the reported incidence of extradural abscess after lumbar extradural analgesia in obstetric patients, as pointed out by Drs Kitching and Rice. However, these populations are not equivalent. Closer inspection of reports within the general population demonstrates a high incidence of co-existing chronic disease, which is a risk factor for compromised immunity, and a predilection for the older age group, the majority of cases being patients older than 50 yr [2, 3]. In contrast, the average parturient is young and relatively healthy compared with the general population. Therefore a direct comparison of relative incidence between the obstetric population and the general population is inappropriate and statistically unsound.

I believe there is strong evidence of a causal relationship between the use of extradural anaesthesia and the development of an extradural abscess in our patient. This is supported by a close temporal relationship, correspondence of the location of the abscess and the site of extradural catheter insertion, and growth of the likely infective organism from a skin lesion at the puncture site.

Whilst Drs Kitching and Rice have demonstrated that extradural abscess can develop in the puerperium without obvious cause, I believe that extradural catheterization remains a risk factor for development of this serious condition in obstetrics and in other specialties, and would reiterate the importance of meticulous aseptic technique when performing these procedures.

Drs Vasdev and Leicht make pertinent comments regarding aseptic technique for extradural catheter insertion. However, I would draw to attention possible neonatal complications that may arise from maternal transdermal absorption of iodine from iodine-containing skin disinfectants. Neonatologists in our institution have shown recently that mothers exposed to topical iodine-containing antiseptics immediately before delivery had concentrations of iodine in their breast milk twice those of non-exposed mothers, and that this appeared to be linked to an increased incidence of transient neonatal hypothyroidism [4]. Iodine absorption would probably be minimized by the practice of rinsing off the iodine with 70% alcohol as recommended by Vasdev and Leicht, but in our delivery suite it is now policy to avoid completely the use of iodine-containing skin disinfectants.

We have favoured polyurethane dressings such as Tegaderm (3M) as dressings for extradural catheter sites because of their excellent fixation properties. Vasdev and Leicht cite evidence that these dressings may increase bacterial colonization, which indeed is of concern; we are currently reappraising usage in our practice.

W. D. Ngan Kee
Wellington School of Medicine
Wellington, New Zealand

1. Male CG, Martin R. Puerperal spinal epidural abscess. *Lancet* 1973; **1**: 608–609.
2. Hlavin ML, Kaminski HJ, Ross JS, Ganz E. Spinal epidural abscess: a ten-year perspective. *Neurosurgery* 1990; **27**: 177–184.
3. Danner RL, Hartman BJ. Update of spinal epidural abscess: 35 cases and review of the literature. *Reviews of Infectious Diseases* 1987; **9**: 265–274.
4. Tracey MB, Richardson VF. Breast milk iodine levels and maternal iodine exposure. The cause of transient neonatal hypothyroidism? *Paediatric Society of New Zealand Annual General Meeting*, October 16, 1991.

THE LARYNGEAL MASK AND INTRAOCULAR SURGERY

Sir,—We were interested in the article of Lamb, James and Janicki on the effect of the laryngeal mask airway (LMA) [1] on intraocular pressure [2]. In their conclusion, the authors mentioned the potential risk of loss of airway control with the LMA during general anaesthesia for intraocular surgery. This risk is not theoretical, but a practical disadvantage of the method, as the anaesthetist does not have access to the patient's airway during surgery.

We describe two patients who recently underwent intraocular surgery under general anaesthesia (thiopentone, fentanyl, enflurane in an oxygen–nitrous oxide mixture and vecuronium). In both patients, insertion of the LMA was easy and resulted in a tight seal, which allowed mechanical ventilation (with peak inspiratory pressure less than 15 cm H_2O) [3]. The LMA was secured with adhesive strips. The surgical procedure for the first patient was initially uneventful, but the LMA was displaced slightly toward the end of the procedure. This resulted in a massive gas leak that led to a dramatic decrease in the expiratory tidal volume (less than 100 ml). Airway control was resumed temporarily by pushing down the LMA, but the leak recurred almost immediately. The LMA was then held in place by the anaesthetist's hand under the drapes and this allowed completion of the procedure. Hypoxia was not detected by pulse oximetry. Recovery was uneventful. In the second patient, a gas leak became evident before the beginning of the procedure, but after drapes, instrumentation and microscope were in place. Because expiratory flow was not detected in the breathing system, the drapes were removed hurriedly. The LMA was removed, the patient's lungs were ventilated using a face mask, additional thiopentone (150 mg) given i.v. and the trachea intubated. Hypoxia was not detected. In both patients there were no harmful consequences.

We had chosen to control the airway during general anaesthesia for intraocular surgery with the LMA because, as Lamb, James and Janicki have shown, this could blunt any increase in intraocular pressure. However, a minor incident (displacement of the LMA) could be transformed into a potentially disastrous accident. In our opinion, the inability of the anaesthetist to gain convenient control of the patient's airway during the procedure is a major hazard. Because of our experience, we have discontinued the use of an LMA for airway control in intraocular surgery.

J. Ripart
R. Cohendy
J.-J. Eledjam
Centre Hospitalier Universitaire de Nîmes
F 30029, Nîmes, France

1. Brain AIJ. The laryngeal mask. A new concept in airway management. *British Journal of Anaesthesia* 1983; **55**: 801–805.
2. Lamb K, James MFM, Janicki PK. The laryngeal mask airway for intraocular surgery: effects on intraocular pressure and stress responses. *British Journal of Anaesthesia* 1992; **69**: 143–147.
3. Benumof JL. Laryngeal mask airway: indications and contraindications. *Anesthesiology* 1992; **77**: 843–846.

BRAIN PARTIAL PRESSURES OF ISOFLURANE AND NITROUS OXIDE

Sir,—We read with interest the article by Dr Thornton and colleagues [1], but wish to comment on the methods used. Thornton's group used isoflurane or nitrous oxide, changed randomly in three consecutive 10-min periods. They do not state which anaesthesia system or what fresh gas flows they used.

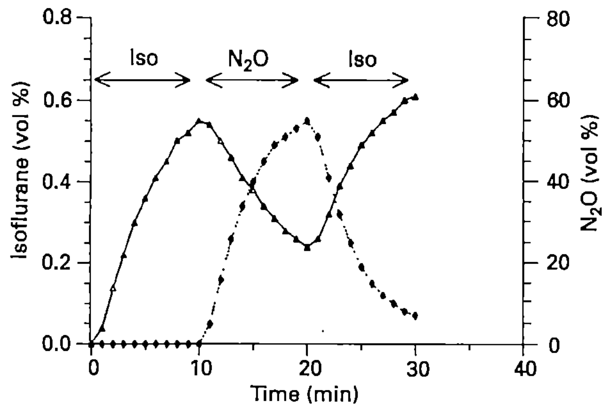


FIG. 1. Computer simulation of the brain partial pressures of isoflurane (△) and nitrous oxide (◆) during three 10-min periods in which either isoflurane (0.65–0.70 % end-tidal) or nitrous oxide (60–65 % end-tidal) was administered. Time = Time after beginning of anaesthesia. Iso = Isoflurane.

We have simulated an isoflurane–nitrous oxide–isoflurane anaesthesia period as described by Thornton and colleagues, with the GUS computer simulation program (Gas Uptake Simulation, iMedEd Inc, Phoenix, Arizona, U.S.A.) using a circle system and fresh gas flows of 12 litre min^{-1}. We agree that, when changing from isoflurane to nitrous oxide after the first 10-min period, stable end-tidal nitrous oxide values can be obtained within 5 min, after which the end-tidal partial pressure of isoflurane would not be less than 5 % of the initial value as stated by Dr Thornton and colleagues, but 0.23 vol % decreasing to 0.15 vol % at the end of the nitrous oxide period. Even with fresh gas flows of 20 litre min^{-1}, the residual end-tidal isoflurane washout from the brain would be even slower (fig. 1). Five minutes after the change from isoflurane to nitrous oxide, the brain partial pressure would be 0.38 vol %, decreasing to 0.24 vol % at the end of the nitrous oxide period. When, as in the first 10-min period, the end-tidal concentration of isoflurane is changed from 0 to approximately 0.70 vol %, a 10-min equilibration period does not produce stable brain partial pressures of isoflurane.

We would recommend longer equilibration periods in order to obtain stable conditions before measurements are performed.

S. PETERSEN-FELIX
A. M. ZBINDEN
University of Berne
Switzerland

1. Thornton C, Creagh-Barry P, Jordan C, Luff NP, Doré CJ, Henley M, Newton DEF. Somatosensory and auditory evoked responses recorded simultaneously: differential effects of nitrous oxide and isoflurane. *British Journal of Anaesthesia* 1992; **68**: 508–514.

Sir,—Thank you for inviting us to reply to the interesting letter from Drs Petersen-Felix and Zbinden. We have used a similar program, Narkup [1], which was produced at Northwick Park, to reproduce exactly the brain concentrations shown in their figure, when the alveolar concentrations of isoflurane and nitrous oxide were maintained at 0.6 % and 60 %, respectively. Clearly, both these programs use, for modelling of the "brain compartment", blood flow, mass and partition coefficient based on whole brain values. This is a good example of the need to know exactly what assumptions are made in pharmacokinetic models. When Narkup is re-run using, for example, assumptions that the effect compartment is in the cerebral grey matter (40 % of the brain), with a high proportion of the blood flow (say 70 %), then brain concentrations are stable for the whole of the test periods. Of course, we have no means of knowing if the above assumptions are true, but the writers of each program also do not know.

The end-expiratory concentrations of both gases were measured directly either by the Capnomac, or by a mass spectrometer in both our 1992 paper, and a previous study which used the same methodology [2]; in both studies, end-expiratory concentration had decreased to less than 5 % of the original concentration before the test period for the next gas. The anaesthetic was delivered from a Manley MP3 (non-rebreathing) as a circle system would have been inappropriate to produce the rapid changes in concentration that we needed. Again, any computer modelling would be dependent on assumptions about minute volume and cardiac output.

The particular point about the three-period statistical construction that we chose [3] is that it effectively eliminates errors which are caused by carry-over from one period to another.

C. THORNTON
D. E. F. NEWTON
Northwick Park Hospital
Harrow

1. Lockwood GG, White DC. Effect of ventilation and cardiac output on the uptake of anaesthetic agents from different breathing systems: A theoretical study. *British Journal of Anaesthesia* 1991; **66**: 519–526.
2. Newton DEF, Thornton C, Creagh-Barry P, Doré CJ. Early cortical evoked response in anaesthesia: comparison of the effects of nitrous oxide and isoflurane. *British Journal of Anaesthesia* 1989; **62**: 61–65.
3. Ebbutt AF. Three period crossover designs for two treatments. *Biometrics* 1984; **40**: 219–224.

HYPERTONIC SOLUTIONS IN MASSIVE HAEMORRHAGE

Sir,—We read with interest the case report by Dr Ngan Kee and transfusion by Donaldson, Seaman and Park [1] and would commend the authors on providing the reader with an excellent practical approach to the initial management of the acutely bleeding, hypovolaemic patient. However, we feel that a discussion on the crystalloid/colloid controversy should also now include some comment on the use of hypertonic solutions.

As the authors state, the success of initial resuscitation in the acutely hypovolaemic patient depends upon speed and adequacy of repletion. There has been increasing interest in the use of hypertonic solutions in the prehospital management of patients with traumatic hypovolaemic shock [2, 3]. The advantage of hypertonic over isotonic solutions in early resuscitation is that adequate resuscitation can be accomplished rapidly with small volumes through peripheral i.v. lines until conventional fluid therapy can be initiated. The smaller volume of fluid may also reduce complications related to dilutional coagulopathy and thermal stress. Hypertonic saline–Dextran 70 has been shown to improve mean arterial pressure, cardiac output, oxygen delivery and urine output and to increase survival compared with Ringer's lactate solution in severely traumatized patients [3].

Hypertonic solutions are still at an early stage of clinical investigation and further work is required before their role in fluid resuscitation is evaluated fully [4, 5]. The anticipated problems of acute hypernatraemia, hypervolaemia and venous injury have not materialized in the studies published so far [4].

We would suggest that in acute massive haemorrhage where venous access may be limited and rapid restoration of arterial pressure is required, there may be a role for hypertonic solutions. We would be interested in the authors' views on this subject.

J. BRIMACOMBE
A. BERRY
Royal Perth Hospital
Perth, Australia

1. Donaldson MDJ, Seaman MJ, Park GR. Massive blood transfusion. *British Journal of Anaesthesia* 1992; **69**: 621–630.
2. Mattox KL, Maningas PA, Moore EE. Prehospital hypertonic saline/dextran infusion for post-traumatic hypotension. *Annals of Surgery* 1991; **213**: 482–489.
3. Holcroft J, Vassar M, Turner J. 3 % NaCl and 7.5 % dextran 70 in the resuscitation of severely injured patients. *Annals of Surgery* 1987; **206**: 279–288.
4. Dontigny L. Small-volume resuscitation. *Canadian Journal of Surgery* 1992; **35**: 31–33.
5. Vincent J-L. Fluids for resuscitation. *British Journal of Anaesthesia* 1991; **67**: 185–193.

Sir,—We are grateful to Drs Brimacombe and Berry for pointing out the omission of a discussion about hypertonic solutions. These authors have eloquently stated the advantages for hypertonic solutions and I agree with them. However, as they say, these solutions are still at an early stage of clinical investigation and I would further agree that more work is needed before they can be recommended routinely.

G. R. Park
Addenbrooke's Hospital
Cambridge

METAL PARTICLE GENERATION CAUSED BY THE COMBINED SPINAL–EXTRADURAL TECHNIQUE

Sir,—Recent letters in this journal [1, 2] have raised the question of potential damage to spinal or extradural needles when the needle-through-needle combined spinal–extradural technique is used. It has even been suggested that metal particle generation may arise because of this method [3].

Portex Ltd would like to take the opportunity to inform clinicians of an independent evaluation conducted to investigate this issue [4]. The aims of the study were: to assess any damage to the spinal and extradural needles produced by this technique; and to determine if the technique produces metal particulate contamination.

The trial tested the technique against different variables which could occur in clinical practice: two types of 26-gauge spinal needle with different tip profiles (lancet or pencil point); two different sizes of Portex Tuohy needles (16- and 18-gauge); two different rotations of the spinal needle during insertion (0° and 360°).

Each type of spinal needle was inserted through a Tuohy needle as during the needle-through-needle technique. A new spinal and extradural needle set was used in each case. When the lancet version was tested, it was introduced with the leading edge "running along" the base of the Tuohy curve in order to maximize any possible scraping effect.

Five millilitre of 0.45–0.8 µm-filtered sterile saline was flushed through the Tuohy needle under test and collected on a 0.45-µm membrane filter. A control sample of saline was taken also. Each membrane was examined under an Olympus BH binocular light microscope with × 10 objective. Any particles present were counted and sized.

Identification of any particles found on the membranes was made by energy dispersive x-ray analysis (EDX) in conjunction with a scanning electron microscope: the electron beam in the microscope strikes a surface and generates x-rays which have energy levels characteristic of the chemical elements present in the surface. The x-rays are detected and plotted out as energy level spectra which carry peaks which may be related unambiguously to specific elements. The technique is semi-quantitative, in that peak heights give an indication of the amount of each element present.

Stainless steel particles are easily recognized using EDX analysis, by their high chromium content. Both the extradural and spinal needles are made from medical grade stainless steel; however, none of the spectra generated indicated the presence of stainless steel particles.

The study showed no evidence to support the supposition that metal particles are produced as a consequence of utilizing the needle-through-needle technique.

Subsequent examination of both spinal and Tuohy needle tips showed no damage attributable to the technique.

J. Hargreaves
Senior Product Manager
Portex (U.K.) Ltd
Hythe, Kent

1. Brownridge P. Spinal anaesthesia in obstetrics. *British Journal of Anaesthesia* 1991; 67: 663.
2. Eldor J. Combined spinal–extradural anaesthesia in obstetrics. *British Journal of Anaesthesia* 1992; 68: 634–635.
3. Eldor J, Brodsky V. Danger of metallic particles in the spinal–epidural spaces using the needle-through-needle approach. *Acta Anaesthesiologica Scandinavica* 1991; 35: 461.
4. Institute for Biomedical Equipment Evaluation and Services, Sheffield University and Health Authority (Lodge Moor Hospital, Sheffield S10 4LH). Report No. R301; May 22, 1992.

FRACTIONAL UTILIZATION OF FRESH GAS BY BREATHING SYSTEMS WITHOUT CARBON DIOXIDE ABSORPTION

Sir,—We have been following with interest the articles by Drs Beatty, Meakin and Healy and their colleagues [1–3] concerning analysis of an Ohmeda EAR system, as we ourselves are analysing the fresh gas utilization of breathing systems without carbon dioxide absorption. The authors of these articles have termed this "fractional utilization" (Fu) of fresh gas. The fresh gas utilization of any system has to be calculated as the fraction of the fresh gas delivered to the patient against the total fresh gas flow into the system. This is independent of patient characteristics and is determined only by the physical characteristics of the system.

We have been calculating the fresh gas utilization of breathing systems without carbon dioxide absorption by first calculating the fraction of fresh gas that does not reach the patient, but is wasted in the system. This fresh gas wastage is calculated using the equation:

$$\frac{P\bar{\mathrm{E}}\mathrm{t}_{\mathrm{CO}_2} - P\bar{\mathrm{E}}\mathrm{v}_{\mathrm{CO}_2}}{P\bar{\mathrm{E}}\mathrm{t}_{\mathrm{CO}_2}} \qquad (1)$$

where $P\bar{\mathrm{E}}\mathrm{t}_{\mathrm{CO}_2}$ = mean expired carbon dioxide tension at the tracheal tube end of the system; $P\bar{\mathrm{E}}\mathrm{v}_{\mathrm{CO}_2}$ = mean expired carbon dioxide tension at the valve end of the system.

The change in the mean expired carbon dioxide tension at the valve end of the system is caused only by dilution of the expired gas by the fresh gas that has come out of the system without reaching the patient.

This equation is similar to that used for calculating the physiological deadspace, in which the fraction of gas that has diluted the ideal alveolar gas is calculated:

$$\frac{V\mathrm{D}}{V\mathrm{T}} = \frac{P\mathrm{a}_{\mathrm{CO}_2} - P\bar{\mathrm{E}}_{\mathrm{CO}_2}}{P\mathrm{a}_{\mathrm{CO}_2}} \qquad (2)$$

The fresh gas utilized by the system (Fu) is the fraction of fresh gas that is not wasted, but reaches the patient and is calculated as:

$$F\mathrm{u} = 1 - \frac{P\bar{\mathrm{E}}\mathrm{t}_{\mathrm{CO}_2} - P\bar{\mathrm{E}}\mathrm{v}_{\mathrm{CO}_2}}{P\bar{\mathrm{E}}\mathrm{t}_{\mathrm{CO}_2}} \qquad (3)$$

Rewriting the above equation, we get

$$F\mathrm{u} = \frac{P\bar{\mathrm{E}}\mathrm{v}_{\mathrm{CO}_2}}{P\bar{\mathrm{E}}\mathrm{t}_{\mathrm{CO}_2}} \qquad (4)$$

The value $P\bar{\mathrm{E}}\mathrm{t}_{\mathrm{CO}_2}$ can be taken as the same as the end-tidal carbon dioxide tension. $P\mathrm{Ev}_{\mathrm{CO}_2}$ can be measured easily by attaching a corrugated tube and an open-ended reservoir bag to the scavenging port of the valve and sampling continuously from the tail end of the bag.

The authors of the above mentioned articles have used complicated calculations from data collected by equally complicated means to derive the fractional utilization of fresh gas of the EAR system. They have analysed the fraction of fresh gas that takes part in the alveolar gas exchange by using the equation:

$$F\mathrm{u} = \frac{\dot{V}_{\mathrm{CO}_2}}{\dot{V}\mathrm{F} \times F\mathrm{A}_{\mathrm{CO}_2}} \qquad (5)$$

This fraction is not determined by the physical characteristics of the breathing system, but by many factors such as age of the patient, smoking, lung pathology, $\dot{V}/\dot{Q}$ mismatch. This should be termed the fractional utilization by the patient, and not by the system.

The authors have shown how variations in patient utilization adversely affect the calculated Fu of the system, in their studies using the EAR system in adults, children and lung models.

In their recently published article [4], they seem to have understood the problems encountered by their approach and have tried to correct it by coining a new term—fractional delivery of fresh gas (Fd)—which is actually the same as the fractional utilization of fresh gas by the system. Here again, they have used a complicated equation:

$$F\mathrm{d} = \frac{\dot{V}_{\mathrm{CO}_2}}{\dot{V}\mathrm{F} \times F\bar{\mathrm{E}}'_{\mathrm{CO}_2}} \qquad (6)$$

They have derived $\dot{V}_{CO_2}$ by accurately measuring the fresh gas flow and multiplying it by $F\bar{\mathrm{E}}\mathrm{v}_{CO_2}$. $F\mathrm{E}'_{CO_2}$ is taken to be the same as the end-tidal carbon dioxide concentration.

Expanding equation (6) we get:

$$Fd = \frac{\dot{V}\mathrm{F} \times F\bar{\mathrm{E}}\mathrm{v}_{CO_2}}{\dot{V}\mathrm{F} \times F\mathrm{E}'\mathrm{t}_{CO_2}} \tag{7}$$

$$= \frac{P\bar{\mathrm{E}}\mathrm{v}_{CO_2}}{P\bar{\mathrm{E}}\mathrm{t}_{CO_2}} \tag{8}$$

It is apparent that equations (4) and (8) are the same. These values can be obtained easily using the same side-stream analyser; accurate measurement of the fresh gas flow is not necessary.

In view of this simplicity, the authors should change their equation to the simpler one. Using two terminologies is confusing and we think that they should use the well accepted terminology of fractional utilization of fresh gas (*F*u) of the system.

M. Ravishankar
S. Chatterjee
Jipmer,
Pondicherry, India

1. Droppert PM, Meakin G, Beatty PCW, Healy TEJ. Fresh gas requirements of an enclosed afferent reservoir breathing system during controlled ventilation. *British Journal of Anaesthesia* 1991; **66**: 638–642.
2. Meakin G, Jennings AD, Beatty PCW, Healy TEJ. Fresh gas requirements of an enclosed afferent reservoir breathing system during controlled ventilation of children. *British Journal of Anaesthesia* 1992; **68**: 43–47.
3. Jennings AD, Mitchell BC, Beatty PCW, Meakin G, Healy TEJ. Physical charcteristics of an enclosed afferent reservoir breathing system. *British Journal of Anaesthesia* 1992; **68**: 625–629.
4. Beatty PCW, Meakin G, Healy TEJ. Fractional delivery of fresh gas: a new index of efficiency of semiclosed breathing systems. *British Journal of Anaesthesia* 1992; **69**: 474–477.

Sir,—Thank you for the opportunity of replying to the letter by Drs Ravishankar and Chatterjee.

The purpose of our paper [1] was to draw attention to the fact that fractional utilization of fresh gas (*F*u) with a semi-closed breathing system is not constant, but varies with the arterial to end-tidal carbon dioxide partial pressure difference of the patients being studied. We noted that if end-tidal carbon dioxide measurements were used in place of arterial measurements in the equations for *F*u, a different parameter resulted which was independent of patient factors. This we termed fractional delivery of fresh gas (*F*d), as it was a measure of the proportion of fresh gas delivered to the patient's alveolar compartment, whether or not it took part in gas exchange.

Drs Ravishankar and Chatterjee have used a different approach than ours to arrive at an equation for calculating breathing system efficiency from measurements of end-tidal and mixed vented carbon dioxide concentrations (equations (1)–(4)). However, as arterial measurements of carbon dioxide are not used, we suggest that the efficiency index they have calculated is fractional delivery and not fractional utilization of fresh gas. This explains why, when simplified, both their equation (3) and ours for *F*d (6) yield the same result (8).

P. C. W. Beatty
G. Meakin
T. E. J. Healy
University of Manchester
Manchester

1. Beatty PCW, Meakin G, Healy TEJ. Fractional delivery of fresh gas: a new index of efficiency of semiclosed breathing systems. *British Journal of Anaesthesia* 1992; **69**: 474–477.

British Journal of Anaesthesia 1993; **70**: 708–709

BOOK REVIEWS

Anesthésie et Analgésie en Obstétrique. Collection d'Anesthésiologie et de Réanimation, Volume 33. Edited by P. Schoeffler. Published (1992) by Masson. Pp. 254; indexed; illustrated. Price FFr. 290.

This volume (No. 33) of the *Collection d'Anesthésiologie et de Réanimation* is the latest addition to the range of text books on obstetric analgesia and anaesthesia. It consists of 13 chapters written by 21 contributors and is divided into four sections.

The first section covers the preoperative anaesthetic assessment of the pregnant woman and the specific problems related to the physiological effects of pregnancy.

The second section, Anaesthetic Management Before and During Pregnancy, consists of four chapters discussing management for oocyte retrieval and *in vitro* fertilization, non-obstetric surgery, fetal surgery and termination of pregnancy.This section is well written and is of current interest because of the introduction of pharmacological methods of terminating early pregnancy. The chapter on anaesthesia and monitoring for fetal intervention discusses the anaesthetic, tocolytic and surgical management to maximize fetal neonatal survival.

The third section, Anaesthesia and Analgesia for Labour, Comprises four chapters which are concise and clear. The chapter on the anaesthetic implications of co-existing diseases in the parturient is excellent and well referenced.

The last section, an overview of the management of maternal and fetal complications, consists of three chapters. The management of pregnancy-induced hypertension and of haemorrhage is discussed thoroughly.

Although this is a relatively small book, it should prove useful to all French speaking anaesthetists. Many of the references are as recent as 1990/91.The volume can be recommended as a useful basis and reference source for those with an interest in obstetric anaesthesia.

B. Appadu

Transesophageal Echocardiography. Edited by F. M. Clements and N. P. de Bruijn. Published by Little, Browne and Co., Boston, Toronto, London. Pp. 163; indexed; illustrated. Price £65.

Conventional transthoracic echocardiography requires considerable operator skill to identify the necessary windows to the heart. Imaging from the chest wall is frequently unsuccessful in patients with emphysema and obesity. In addition, the distance from the transducer located on the chest wall to the left atrium and left ventricle may limit the diagnosis of atrial septal defects, the detection of atrial thrombi and the source of systemic embolization, and the assessment of mitral valve structures and function.

The technical difficulties involved in positioning the transducer in the oesophagus, adjacent to the left chambers, was overcome in 1981 by Hanrath and colleagues in West Germany, when an oesophageal, phased array transducer, capable of two-dimensional imaging, was developed by housing the transducer inside a flexible gastroscope from which the fibreoptics were removed. The development of Doppler colour flow mapping to visualize blood flow velocity within the heart and surgical interest in mitral valve repair were two catalysts in the mid 1980s responsible for the impressive growth and interest in intraoperative transoesophageal echocardiography (TOE).

The technique of TOE entered the sphere of anaesthetic practice in 1985. Drs de Bruijn and Clements from Duke University Medical Centre, Durham, North Carolina, were the first to review comprehensively the basic concepts of this new technology in the anaesthetic literature; furthermore, they edited the Society of Cardiovascular Anesthesiologists' monograph on the intraoperative use of echocardiography. It was inevitable that they would provide a basic text to highlight the technical applications and limitations of TOE. Drs Clements and de Bruijn's first edition *Transesophageal Echocardiography* combines the features of a textbook and an atlas. The 158 pages of text include 10 chapters featuring the development of transoesophageal imaging; two dimensional echocardiography: creating an image; Doppler echocardiography; anatomical orientation to oesophageal imaging; technique of transoesophageal imaging in awake and anaesthetized patients; intraoperative monitoring for regional wall motion abnormalities; evaluation of left ventricular size and function; interventional echocardiography and the mitral valve, the aorta and aortic valve; imaging the right and left atria and atrial and ventricular septal defects. The text in each chapter is accompanied by illustrations, figures, flow charts, line drawings and reproductions of TOE monitor views.

Transoesophageal echocardiography is a technology which spans the spectrum of cardiology, anaesthesia and cardiac surgery. The role of TOE in anaesthetic practice and the educational and technical experience necessary to undertake the procedure continue to evolve, but differ from institution to institution and from year to year. The extent and adequacy of experience with echocardiography is a major concern in 1993 because non-cardiologists, including anaesthetists and surgeons, are currently using the technology for intraoperative clinical decision making with little or no formal training. The mechanisms whereby Cardiac Anaesthesia Fellows in Duke University obtain the satisfactory experience proposed by the American Society of Echocardiography Committee for Physician Training in Echocardiography is outlined briefly in chapter 1.

This reviewer is aware of no better explicit and succinct descriptions of the basic concepts of echocardiography and Doppler colour flow imaging than are presented in chapters 2 and 3. The authors assume the reader has no previous knowledge of these topics. The principles of ultrasound frequency and reflection, transducer design and image processing are described, with additional practical details for the operator such as gain control, depth and width controls, grey scale adjustment, time–gain–compensation (TGC) control and the controls for pulsed-wave Doppler and Doppler colour flow imaging. The authors, fortuitously, featured the Hewlett–Packard console and transducer—the product which has achieved the most extensive anaesthetic application. The artefacts to which the technology is subject and such phenomena such as "echo drop out" and "frequency aliasing" are highlighted.

Chapters 4 and 5 describe the technique of TOE imaging in awake and anaesthetized patients, with special emphasis on how to obtain the base of the heart short axis view, the long axis four-chamber view and the transgastric short axis image of the left and right ventricles. The indications, contraindications and complications of TOE are discussed in detail.

The application of TOE in anaesthetic practice will vary depending on individual interest and practice. Many anaesthetists would welcome a simple-to-use echocardiographic monitoring system which would allow non-invasive assessment of global left ventricular function and regional wall motion. The application of TOE-derived regional wall motion abnormalities in the detection of intraoperative myocardial ischaemia is addressed in chapter 6. If I have any reservations concerning this first edition, it would be that the authors did not balance their interest in TOE as a diagnostic tool with, perhaps, its more useful anaesthetic relevance as a non-invasive monitoring technique. For example, segmental wall motion scoring systems are referred to, but not described. Somewhat superficial comparisons were made between the sensitivity of regional wall motition abnormalities and ECG-derived ST segment and pulmonary artery occlusion pressure changes. The techniques to assess left ventricular end-diastolic area as an index of preload, left ventricular area ejection fraction as an index of left ventricular performance and left ventricular wall stress are described, but no data are provided about validation studies of these measurements and their potential intraoperative and critical care applications. Also, no references were provided for this and some other chapters.

The interest of the authors in transoesophageal echocardiography as a diagnostic tool was highlighted by the statement... "the single most useful application of TEE is the study of mitral regurgitation". The role of Doppler colour flow imaging in the evaluation and quantification of mitral regurgitation, the detection of paravalvular leaks and the adequacy of surgical results are all discussed and illustrated in impressive detail. Similarly, a comparative evaluation is provided of TOE, as compared with angiography and computed tomography in the evaluation of dissection of the ascending and descending aorta. That anaesthetists could, or should, be involved in these diagnostic deliberations is a matter of debate.

The application of transoesophageal echocardiography in clinical practice has shown impressive growth and striking regional variations over the past decade. TOE has now become a mandatory integral component of mitral valve repair in many North American institutions. Individual anaesthetists in North American and continental Europe have increasingly used TOE as a monitoring adjuvant during aortocoronary bypass surgery, major vascular surgery and posterior fossa surgery with the patient in the sitting position. In contrast, United Kingdom anaesthetists, whether for economic considerations or because of adherence to more traditional "finger on the pulse" clinical assessment, have tended to ignore this new technology and British experience, to date, has been mostly confined to cardiological studies in awake patients. Notwithstanding, this first edition of *Transesophageal Echocardiography* by Clements and de Bruijn is a must for any practitioner—cardiologist, cardiac surgeon or anaesthetist—involved in the management of patients undergoing major cardiac or vascular surgery or critical care medicine.

A. J. Cunningham

The Complete Recovery Room Book. By A. Hatfield and M. Tronson. Published by Oxford University Press, Oxford. Pp. 369; indexed; illustrated. Price £17.50.

This book is presented as a comprehensive reference manual for recovery rooms, and is a further addition to recently published texts on the immediate postoperative care of surgical patients. It comprises three main sections: "Setting up a Recovery Room", "Patient Care" and "Basic Physiology and Useful Data".

The opening chapters of the first section deal with the physical design and staffing of the recovery room. These may be of interest to some readers, but is probable that the third chapter will be more useful, as it gives an excellent functional description of the basic items of equipment used by recovery room staff. The closing chapter in this section is a welcome appraisal of the importance of preventing cross-infection in the recovery room.

The second section, "Patient Care", is an exposition of the immediate care of patients after operation. This is well written and comprehensive. For example, the chapter "Routine recovery room procedures" is an excellent and practical introduction to the subject, although I cannot accept that awareness under general anaesthesia is a "daily dilemma" as described! Other chapters deal with the assessment of patients, emergencies, monitoring, analgesia, i.v. fluids, bleeding problems and drugs and infusions. This section of the book would be very useful for teaching, and it would be easy to base a tutorial course on it.

The third section of the book is a concise description of cardiovascular and respiratory physiology. The Appendices are useful and include an explanation of abbreviations used in hospitals, a description of pulmonary artery flotation catheters, procedures for assessing patients (Glasgow coma scale), and suggestions for "emergency" trays to be used, for example, for the treatment of anaphylaxis.

It is a little difficult to anticipate who will find this book most attractive. The problem is that, in certain places, the approach is very simplistic (e.g. "the recovery room links the theatres to the wards"), which will not appeal to doctors, but as a whole the book does contain a considerable amount of detailed information. From their Preface, it seems that the authors intended it to be used for the teaching of nursing staff, and I would suggest that it would be best used as a core textbook for an introductory course on recovery room techniques.

I. Power

Essay Plans for Anaesthesia Exams. By M. Z. Michel, N. W. Goodman and A. R. Aitkenhead. Published by Churchill Livingstone, Edinburgh. Pp. 191; indexed. Price £15.95.

The authors of this short book state that it originated from the preparation of one of the authors for the Part 3 examination. He made essay plans for previous, and predicted, questions and these plans form the basis of the present volume. The book is intended for candidates for the Parts 1 and 3 of the F.R.C.A. examination, although I expect that its main appeal will lie with those taking Part 3. It contains outline answers to 75 questions, with advice on common errors.

The book is divided into seven chapters indicating general areas of interest such as anatomy and regional anaesthesia, intensive care, specialized general anaesthesia and questions based on physiology and pharmacology. Within each chapter, between eight and 16 outline answers to specific questions are provided. The approach is didactic, with clear advice as to what is correct and what is incorrect. I found myself in agreement with most of the outlines provided, although in my areas of specific interest there are some small factual errors. I doubt if they would influence the examination mark awarded, but they do illustrate the point that it is no longer possible for an author, or three authors, to keep up with current knowledge in all areas of anaesthetic practice. Indeed, many of us who teach extensively for the examinations adopt a two-handed approach. We teach the safe examination answer and the current state of knowledge; regrettably there is often a considerable gulf between the two.

I expect that this book will be successful, as it fulfils a need of many examination candidates. I hope that the essay questions remain an important part of our examination structure. Anaesthetists must be able to demonstrate that they can apply their knowledge logically and sensibly to common clinical problems. Michel, Goodman and Aitkenhead will help many candidates to improve their written presentation.

G. M. Hall

ERRATA

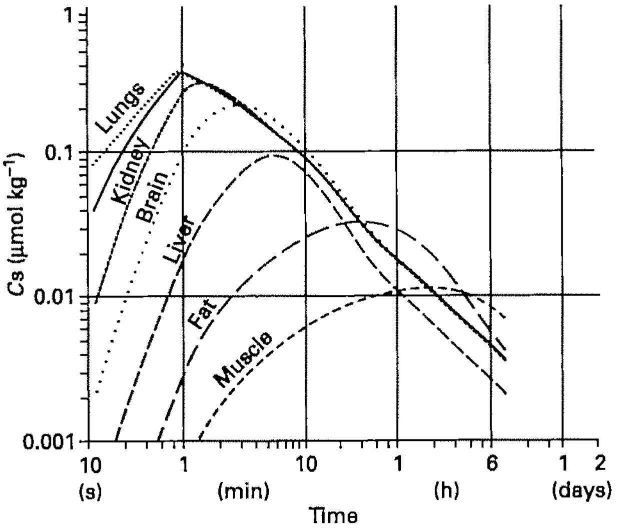
British Journal of Anaesthesia 1993; **70**: 25–29

In the legend to figure 2 of this article, the symbols for P1 and P2 are transposed. The legend should read:

FIG. 2. The pressure–volume curves for P1 (●), P2 (▲), P3 (△) and P4 (○) for (A) size 2, (B) size 3 and (C) size 4 laryngeal mask airways, in 10 patients unless indicated otherwise.

British Journal of Anaesthesia 1993; **70**: 248–258

The typesetters and technical editor (S.L.) wish to apologize to Dr Davis and Professor Mapleson for a combination of errors and oversights which led to publication of an obsolete version of figure 9 in the above paper (p. 255). The correct version is reproduced below (the legend as published is correct).



AUTHOR INDEX

VOLUME 70, 1993

British Journal of Anaesthesia

ARS = Anaesthetic Research Society papers
ESA = European Society of Anaesthesiologists (Founding Congress) Abstracts
C = Correspondence
E = Editorial
R = Book review

Abels, R. *see* Faris, P. P., (*ESA*) A.101
Aderjan, R. *see* Motsch, J., (*ESA*) A.155
Ahmad, R., Sami, K. A. and Rabbeah, A. A bifurcated endobronchial tube in the management of laryngotracheo-oesophageal cleft repair 696–698
Aitkenhead, A. R. *see* Hennessy, N., (*ARS*) 475P; Lamb, J. M., (*ARS*) 478–479P; Mahajan, R. P., (*ESA*) A.68; (*ARS*) 482–483P; Michel, M. Z., (*R*) 709
Åkeson, J., Björkman, S. and Messeter, K. Midazolam prevents ketamine-induced stimulation of cerebral metabolism, (*ESA*) A.111
Albanese, J., Viviand, X., Durbec, O., Alliez, B. and Martin, C. Sufentanil increases intracranial pressure in patients with head trauma, (*ESA*) A.107
Alcock, R., Peachey, T., Lynch, M. and McEwan, T. Comparison of alfentanil with suxamethonium in facilitating nasotracheal intubation in day-case anaesthesia 34–37
Alderson, P. J., Burrows, F. A., Stemp, L. I. and Holtby, H. M. Use of ultrasound to evaluate internal jugular vein anatomy and to facilitate central venous cannulation in paediatric patients 145–148
Alfonsi, P., Hongnat, J.-M., Lebrault, C. and Chauvin, M. Fentanyl, as pethidine, inhibits post anaesthesia shivering, (*ESA*) A.74
Al-Hasani, A. Ketorolac postoperative analgesia, (*C*) 112–113
Ali, H. H. *see* Shorten, G. D. 160–162
Ali-Melkkilä, T., Virkkilä, M., Soini, H. and Kanto, J. Pharmacokinetics and effects of i.m. alfentanil as premedication for outpatient cataract surgery, (*ESA*) A.145
Allagain, J. *see* Heath, M. L., (*C*) 596
Allen, J. G. *see* Carroll, P. H., (*C*) 600
Allen, P. *see* Quiney, N. F., (*C*) 380
Allen, P. R. *see* Gilligan, S., (*C*) 491
Alliez, B. *see* Albanese, J., (*ESA*) A.107
Allsop, E. *see* Innes, P., (*ESA*) A.167
Allt-Graham, J. *see* Menon, G. 587–590
Alon, E., Lenzlinger, P. M. and Pasch, T. Ondansetron 4 mg *vs* droperidol 1.25 mg in the prophylaxis of postoperative nausea and vomiting after alfentanil-supplemented inhalation anaesthesia, (*ESA*) A.12
Alon, E. *see* Biro, P., (*ESA*) A.156
Alvarez, J., Camara, M. L., Cortiñas, J., Cortes, J. and Aris, A. Pulmonary and systemic vascular effects of isoproterenol, nitroglycerin and prostaglandin E1 early after cardiac operations in patients with pulmonary hypertension, (*ESA*) A.27
Amaha, K. *see* Saitoh, Y. 402–404
Amantea, B. *see* Santangelo, E., (*ESA*) A.206
Amery, A. *see* Wiebalck, A., (*ESA*) A.90; (*ESA*) A.154
Amilon, A. *see* Rawal, N. 280–285
Anderson, J. *see* Carli, F., (*ESA*) A.86
Anderson, K. *see* Crawford, M. 419–422
Andrade, J. *see* Munglani, R., (*ARS*) 483–484P
Angster, R. *see* Doenicke, A., (*C*) 491
Annat, G. and Clergue, F., (editors) *Collection d'Anesthésiologie et de Réanimation, Volume 30: Monitorage Non-Invasif en Réanimation*, (*R*) 117
Ansermino, J. M. *see* Blogg, C. E., (*C*) 596–597
Appadu, B. Perioperative blood loss, (*C*) 492–493
Appadu, B., Rowbotham, D. J., Griffiths, R., Graham, S. and Norman, R. I. Membrane action of volatile anaesthetics: effect of halothane on microviscosity, (*ARS*) 477P
Arieff, A. I., (editor) *Hypoxia, Metabolic Acidosis and the Circulation*, (*R*) 118
Ariès, J. *see* Arné, J., (*ESA*) A.1
Aris, A. *see* Alvarez, J., (*ESA*) A.27
Armellin, G., Sorbara, C., Pittarello, D., Penzo, D. and Giron, G. P. Acute preoperative plasmapheresis during cardiac surgery, (*ESA*) A.104
Arné, J., Descoins, P., Bresard, D., Ariès, J. and Fusciardi, J. A new clinical score to predict difficult intubation, (*ESA*) A.1
Arnold, B. D. C. Sedation with propofol during regional anaesthesia, (*C*) 112
Arnold, C., Bain, J., Brown, R. A., Harden, R. M., Laidlaw, J. M., McAleer, S. and Wood, R. A. *Moving to Audit, An Educational Package for Hospital Doctors and General Practitioners* 118
Arock, M. *see* Riou, B., (*ESA*) A.103
Aronson, J. K. *see* Graham-Smith, D. G., (*R*) 601
Aronstam, R. S. *see* Martin, D. C. 365–367
Arroyo, J. L. *see* Catalá, J. C., (*ESA*) A.89; Monedero, P., (*ESA*) A.98; de los Ríos, J., (*ESA*) A.75
Arthaud, M. *see* Bodin, L., (*ESA*) A.191
Arthur, D. S. *see* Runcie, C. J. 192–195
Artigas, A., Lemaire, F., Suter, P. M. and Zapol, W. M., (editors) *Adult Respiratory Distress Syndrome*, (*R*) 117
Atcheson, R., Rowbotham, D. J. and Lambert, D. G. Effect of fentanyl on [^{3}H]noradrenaline uptake in isolated neuronal cell preparations, (*ARS*) 485P
Attebo, L., Bengstsson, M. and Johnson, A. Comparison of portable emergency ventilators using a lung model 372–377
Aubert, M. *see* Kozak Ribbens, G., (*ESA*) A.92
Aubrun, F., Narchi, P. and Benhamou, D. Evaluation of pain and analgesia in a postanesthesia care unit, (*ESA*) A.198
Auffray, J.-P. *see* Martin, C., (*ESA*) A.190
Aun, C. S. T., Sung, R. Y. T., O'Meara, M. E., Short, T. G. and Oh, T. E. Cardiovascular effects of i.v. induction in children: comparison between propofol and thiopentone 647–653
Auroy, Y., Gillon, M.-C., Bismuth, H. and Ecoffey, C. Measurement of sigmoid intramural pH during orthotopic liver transplantation, (*ESA*) A.76
Auroy, Y. *see* Descraques, C., (*ESA*) A.127
Aya, G. *see* Lefrant, J. Y., (*ESA*) A.18

Babik, B. *see* Vereczkey, Z., (*ESA*) A.64
Bach, A. *see* Motsch, J., (*ESA*) A.155
Backman, C. *see* Hohner, P., (*ESA*) A.41
Baconnier, P. *see* Py, C., (*ESA*) A.57
Baddeley, A. *see* Munglani, R., (*ARS*) 483–484P
Baer, G. A. *see* Rorarius, M. G. F. 293–297
Bailey, C. R., Ruggier, R. and Findley, I. L. Diamorphine/bupivacaine mixture *vs* plain bupivacaine: a comparison of epidural infusions in labour, (*ESA*) A.169
Bailey, P. M. *see* Williams, P. J. 30–33
Bain, J. *see* Arnold, C. 118
Baker, A. B., McGinn, A. and Joyce, C. Effect on lung volumes of oxygen concentration when breathing is restricted 259–266
Balatoni, E. *see* Zaouk, G., (*ESA*) A.11
Bålfors, E. and Franklin, K. Cerebral perfusion during obstructive sleep apnea (OSA), (*ESA*) A.62
Bålfors, E. *see* Svanström, M., (*ESA*) A.177
Ball, S. P., Dorkins, H. R., Ellis, F. R., Hall, J. L., Halsall, P. J., Hopkins, P. M., Mueller, R. F. and Stewart, A. D. Genetic linkage analysis of chromosome 19 markers in malignant hyperthermia 70–75
Baller, S. *see* Motsch, J., (*ESA*) A.155
Baltás, B. *see* Vereczkey, Z., (*ESA*) A.64
Bannister, J. *see* McLeod, G. A., (*C*) 593
Banssillon, V. *see* Py, C., (*ESA*) A.57

Baranowski, A. P. and Buist, R. J. Peripheral nerve damage and regional anaesthesia, (*C*) 593–594

Bardoczky, G., Engelman, E. and d'Hollander, A. Continuous spirometry: an aid in the intraoperative respiratory monitoring—case reports, (*ESA*) A.55

Bardoczky, G. *see* Engelman, E., (*ESA*) A.56

Bardoczky, G. I., Levarlet, M., Engelman, E. and Defrancquen, P. Continuous spirometry for detection of double-lumen endobronchial tube displacement 499–502

Barker, P. *see* Langton, J. A. 126–130; Murphy, P. J. 131–134

Baron, J.-F. *see* Delayance, S., (*ESA*) A.45; Fellahi, J. L., (*ESA*) A.44

Barré, J. *see* Plaud, B., (*ESA*) A.141

Barrie, J. R., Beatty, P. C. W., Campbell, I. T., Meakin, G. and Healy, T. E. J. Fresh gas requirements of an enclosed afferent reservoir breathing system in anaesthetized, spontaneously breathing adults 468–470

Barsoum, L. Z. *see* Field, L. M. 154–159

Baskett, P. J. F. Death certification, (*C*) 112; Use of lignocaine in ventricular defibrillation? (*C*) 380

Bauch, U. *see* Molter, G. 428–433

Baudot, J., Vertommen, J. D. and Van Aken, H. Patient controlled epidural analgesia *vs* intermittent injections during labor using 0.125% bupivacaine and sufentanil, (*ESA*) A.170

Baurain, M. J., Dernovoi, B. S., d'Hollander, A. A. and Bollen, P. C. Reversal of vecuronium induced neuromuscular blockade: no effects of atropine administration timing, (*ESA*) A.134

Baurain, M. J., Dernovoi, B. S., d'Hollander, A. A. and Schmartz, D. M. Can repetition of high frequencies stimuli alter the value of 50 and 100 Hz tetanic fade during vecuronium induced neuromuscular blockade? (*ESA*) A.135; Comparison between double-burst stimulation and 50, 100 Hz tetanic fade during spontaneous recovery of vecuronium induced neuromuscular blockade, (*ESA*) A.133

Baurain, M. J. *see* Dernovoi, B. S., (*ESA*) A.137

Baxter, J. N. *see* McMahon, A. J., (*C*) 493–494

Bayhan, N., Güzeldemir, M. E. and Türkan, H. The effects of bupivacaine, mepivacaine and prilocaine on platelet aggregation, (*ESA*) A.123

Bayly, P. *see* Phillips, S. 687–688

Bazin, J. E., Gillart, T., Comte, A., Dubray, C. and Schoeffler, P. Does nicardipine potentiate the neuromuscular block of atracurium? (*ESA*) A.136

Beards, S. C. *see* Griffiths, A. G. 223–225

Beatty, P. C. W., Meakin, G. and Healy, T. E. J. Fractional utilization of fresh gas by breathing systems without carbon dioxide absorption, (*C*) 707

Beatty, P. C. W. *see* Barrie, J. R. 468–470

Beaussier, M., Coriat, P., Gosgnach, M., Portilla, M., Kalfon, P. and Viars, P. Determinants of systolic pressure variation in patients ventilated after vascular surgery, (*ESA*) A.37

Beaussier, M. *see* Gosgnach, M., (*ESA*) A.21

Beck, G. N., Masterson, G. R., Richards, J. and Bunting, P. Propofol and alfentanil or thiopentone and suxamethonium for tracheal intubation, (*ARS*) 483P

Bedrossian, J. *see* Jacob, L., (*ESA*) A.85

Beemer, G. H., Bjorksten, A. R. and Crankshaw, D. P. Pharmacokinetic/pharmacodynamic modelling of atracurium, (*C*) 111

Begon, C. *see* Jamali, S., (*ESA*) A.160

Ben Ameur, M. *see* Reignier, J., (*ESA*) A.162

Bengstsson, M. *see* Attebo, L. 372–377

Benhamou, D., Malinowsky, J.-M., Quinquis, V., Bourget, P. and Couarraze, G. Slow-release effect of pH-adjusted bupivacaine: pharmacokinetic demonstration, (*ESA*) A.120

Benhamou, D. *see* Aubrun, F., (*ESA*) A.198; Hamza, J., (*ESA*) A.171; Joly, L.-M., (*ESA*) A.58

Bennet, J., Ramachandra, V. and Carli, F. An investigation into the effect of passive and active cutaneous warming devices on intraoperative body temperature in elderly patients, (*ESA*) A.73

Bennett, S., Nelson, V. and Green, T. Propofol (2,6 diisopropylphenol) as an antioxidant *in-vitro*: a dose response study, (*ESA*) A.152

Bermejo, N., Guéant, J. L., Mata, E., Gérard, P., Moneret-Vautrin, D. A. and Laxenaire, M. C. Platelet serotonin is a mediator potentially involved in anaphylactic reaction to neuromuscular blocking drugs 322–325

Bernaus, M. *see* Fernandez, D., (*ESA*) A.131

Bernière, J. *see* Murat, I., (*ESA*) A.165

Berridge, J. C. Statistical assessment of two methods of clinical measurement, (*C*) 595

Berrisford, R. G., Sabanathan, S., Mearns, A. J., Clarke, B. J. and Hamdi, A. Plasma concentrations of bupivacaine and its enantiomers during continuous extrapleural intercostal nerve block 201–204

Berry, A. *see* Brimacombe, J., (*C*) 381; (*C*) 596; (*C*) 705

Berthoud, M. C., McLaughlan, G. A., Broome, I. J., Henderson, P. D., Peacock, J. E. and Reilly, C. S. Comparison of infusion rates of three i.v. anaesthetic agents for induction in elderly patients 423–427

Bertrand, M. *see* Gosgnach, M., (*ESA*) A.5; (*ESA*) A.6

Bertrix, L. *see* Freysz, M., (*ESA*) A.46

Beydon, L., Rauss, A., Lofaso, F., Harf, A. and Bonnet, F. A survey of sleep problems in surgical patients, (*ESA*) A.4

Beydon, L. *see* Catoire, P., (*ESA*) A.192; Liu, N., (*ESA*) A.128; Mimoz, O., (*ESA*) A.180

Bhatt, S. B. *see* Oh, T. E., (*C*) 237–238; Tan, I. K. S. 267–272

Biber, B. *see* Raner, C., (*ESA*) A.49; Sundeman, H., (*ESA*) A.50

Binning, A. *see* Forbes, D., (*ESA*) A.125

Birkhahn, A. *see* Weiss, M. 317–321

Biro, P., Alon, E., Weidmann, G. and Pietzsch, S. Dose dependent effects of oral medication with midazolam, (*ESA*) A.156

Bismuth, H. *see* Auroy, Y., (*ESA*) A.76

Bitker, M. *see* Mouquet, C., (*ESA*) A.83

Bitker, M.-O. *see* Mouquet, C., (*ESA*) A.82; (*ESA*) A.84

Björkman, S. *see* Åkeson, J., (*ESA*) A.111

Bjorksten, A. R. *see* Beemer, G. H., (*C*) 111

Blin, O. *see* Paut, O., (*ESA*) A.10

Blockmans, D., Van Hemelrijck, J. and Van Aken, H. Ketamine does not prevent hypotension caused by induction of anaesthesia with propofol in elderly patients, (*ESA*) A.40

Blogg, C. E. and Ansermino, J. M. Cricoid pressure and the laryngeal mask airway, (*C*) 596–597

Bock, K. H. *see* Felleiter, P., (*ESA*) A.196

Bodin, L., Laurent, P., Do-Khac, T., Zouaoui, Z., Lamas, G., Cambau, E., Rouby, J. J. and Viars, P. Incidence of bacterial maxillary sinusitis in critically ill patients with radiologic maxillary sinusitis, (*ESA*) A.179

Bodin, L., Maghrebi, H., Kaddour, C., Arthaud, M., Rouby, J. J. and Viars, P. Non invasive monitoring of CO_2 in patients with septic shock, (*ESA*) A.191

Bodin, L. *see* Rouby, J. J., (*ESA*) A.181

Boer, F., Engbers, F., Burm, T., Bovill, J. and Hak, A. Sufentanil first-pass pulmonary uptake at three different steady state concentrations of the drug, (*ESA*) A.147

Boerger, N. *see* Striebel, W. H., (*ESA*) A.210

Böhrer, H. *see* Geiger, C., (*ESA*) A.14

Boldt, J., Knothe, C., Schindler, E., Hammermann, H., Dapper, F. and Hempelmann, G. Volume replacement with hydroxyethyl starch solution in children 661–665

Bollen, P. C. *see* Baurain, M. J., (*ESA*) A.134; Dernovoi, B. S., (*ESA*) A.137

Bonara, Z. *see* Foppoli, R., (*ESA*) A.132

Bonneau, M. *see* Samama, C. M., (*ESA*) A.100

Bonnet, F. *see* Beydon, L., (*ESA*) A.4; Catoire, P., (*ESA*) A.192; Fulgencio, J. P., (*ESA*) A.42; Liu, N., (*ESA*) A.25; (*ESA*) A.128; 515–518; Mimoz, O., (*ESA*) A.180

Bonnin, P. *see* Samama, C. M., (*ESA*) A.100

Boogaerts, J., Lafont, N. and Legros, F. J. Epidural administration of liposomal bupivacaine for the management of postsurgical pain, (*ESA*) A.200

Boogaerts, J. *see* Legros, F. J., (*ESA*) A.122

Booker, P. *see* Innes, P., (*ESA*) A.167

Boosaert, L. *see* Heytens, L., (*ESA*) A.178

Bordenave, L. *see* Janvier, G. 186–191

Borgeat, A., Wilder-Smith, O. H. G., Despland, P. A. and Ravussin, P. Spontaneous excitatory movements during recovery from propofol anaesthesia in an infant: EEG evaluation 459–461

Borissov, B. *see* Smilov, I., (*ESA*) A.176

Borsarelli, J. *see* Kozak Ribbens, G., (*ESA*) A.92

Böttiger, B. *see* Rauch, H., (*ESA*) A.30

Bougnières, P. *see* Menigaux, C., (*ESA*) A.175

Bouillon, R. *see* Wiebalck, A., (*ESA*) A.90; (*ESA*) A.154

Boules, Z. *see* Mirakhur, R. K., (*C*) 235

Bourgain, J. L. *see* Lequeau, F., (*ESA*) A.97

Bourgain, J.-L. *see* Spencer, A., (*ESA*) A.207

Bourget, P. *see* Benhamou, D., (*ESA*) A.120

Bovill, J. *see* Boer, F., (*ESA*) A.147

Bowman, W. C. *see* Braga, M. F. M. 405–410

Boyd, J. T. *see* Lamond, C. T., (*ESA*) A.204

Boys, R. J. *see* Robson, S. C. 634–638

Brady, O. H. *see* Joshi, G. P. 87–88

Braga, M. F. M., Rowan, E. G., Harvey, A. L. and Bowman, W. C. Prejunctional action of neostigmine on mouse neuromuscular preparations 405–410

Brandom, B. W. *see* Meretoja, O. A., (*ESA*) A.140
Bredenkötter, U. *see* Schregel, W., (*ESA*) A.105
Breed, N. *see* Rittoo, D. B., (*ARS*) 486P
Bresard, D. *see* Arné, J., (*ESA*) A.1
Breschinski, W. *see* Felleiter, P., (*ESA*) A.196
Bright, J. *see* Kulkarni, P. 216–218
Brimacombe, J. and Berry, A. Cricoid pressure and the laryngeal mask airway, (*C*) 596; Hypertonic solutions in acute massive haemorrhage, (*C*) 705; Regurgitation and the laryngeal mask airway, (*C*) 381
Brodsky, J. B. *see* Shenkman, Z. 349–359
Bromage, P. R. Spinal extradural abscess: pursuit of vigilance 471–473
Bromberg, N., Decoene, C., Chammas, E., Pol, A. and Krivosic-Horber, R. Echocardiographic study of the induction with a low-dose of sufentanil for coronary artery surgery, (*ESA*) A.28
Broome, I. J. *see* Berthoud, M. C. 423–427
Brown, A. G. *see* Jones, R. D. M. 286–292
Brown, R. A. *see* Arnold, C. 118
Browne, D. *see* Mythen, M., (*ESA*) A.29
Brubakk, A. O. *see* Flook, V., (*ARS*) 474–475P
Bruelle, P. *see* de La Coussaye, J. E., (*ESA*) A.121
de Bruijn, N. P. *see* Clements, F. M., (*R*) 708
Brummer, G. *see* Striebel, W. H., (*ESA*) A.209
Brune, K. *see* Geisslinger, G. 666–671
Bruneval, P. *see* Samama, C. M., (*ESA*) A.100
Brutsaert, D. L. *see* De Hert, S. G., (*ESA*) A.47
Buckmaster, H. A., Kerr, K. A. and Kudynska, J. Spin resonance spectroscopy to detect malignant hyperthermia susceptibility, (*C*) 598–599
Buist, R. J. *see* Baranowski, A. P., (*C*) 593–594
Bunting, P. *see* Beck, G. N., (*ARS*) 483P
Burke, J. F. *see* Lee, R. C., (*R*) 601
Burm, T. *see* Boer, F., (*ESA*) A.147
Burrows, F. A. *see* Alderson, P. J. 145–148
Butscher, K., Mazoit, J. X. and Samii, K. Postoperative analgesia: a two dosage regimens trial for i.m. morphine after early i.v. titration, (*ESA*) A.201

Caen, J. P. *see* Samama, C. M., (*ESA*) A.100
Calappi, E. *see* Mulazzi, D., (*ESA*) A.54
Calmatte, S. *see* Orliaguet, G., (*ESA*) A.163
Calow, P. *see* Myles, A. P., (*ARS*) 476–477P
Calvey, T. N. Synergy and isoboles, (*E*) 246–247
Camara, M. L. *see* Alvarez, J., (*ESA*) A.27
Camarero, A. *see* Martínez Urionabarrenetxea, K., (*ESA*) A.187; Pérez Arancón, J. L., (*ESA*) A.188
Cambau, E. *see* Bodin, L., (*ESA*) A.179
Camboulives, J. *see* Paut, O., (*ESA*) A.10
Campbell, I. T. and Green, C. J. Metabolic effects of dobutamine, (*C*) 236
Campbell, I. T. *see* Barrie, J. R. 468–470; McKavney, M., (*ARS*) 475P; Watt, T., (*ARS*) 477P
Campkin, N. *see* Hood, J. R., (*ARS*) 480P; Law Min, J.-C., (*ARS*) 480–481P
Campkin, N. T. A., Hood, J. R. and Feldman, S. A. Tetanic fade during recovery from vecuronium block: comparison of systemic and isolated forearm administration 581–582
Campling, E. A. *see* Lunn, J. N., (*C*) 382
Camus, Y., Delva, E. and Lienhart, A. Preoperative skin-surface warming reduces intraoperative hypothermia, (*ESA*) A.72
Carayon, A. *see* Mouquet, C., (*ESA*) A.83; (*ESA*) A.84
Carli, F., Anderson, J., Read, M. and Halliday, D. Effect of recombinant human growth hormone (HGH) on protein metabolism in surgical patients, (*ESA*) A.86
Carli, F. *see* Bennet, J., (*ESA*) A.73; Jakeways, M. S. R., (*C*) 597; Kulkarni, P., (*ESA*) A.70; 216–218; McHale, S., (*C*) 701
Carrascosa, F. *see* Hidalgo, F., (*ESA*) A.99; Monedero, P., (*ESA*) A.98
Carrera, J., Monedero, P., Iribarren, M. J., de los Ríos, J. and Panadero, A. Changes in blood lactate, total body oxygen delivery and consumption during liver transplantation, (*ESA*) A.77
Carrera, J. *see* Monedero, P., (*ESA*) A.98
Carrera, J. A. *see* Catalá, J. C., (*ESA*) A.89
Carrie, L. E. S. *see* Uncles, D. R., (*C*) 116
Carroll, P. H. and Allen, J. G. Pain relief after anterior cruciate ligament repair, (*C*) 600
Carson, D. *see* McLeod, G. A., (*C*) 593
Casey, K. R. *see* Reeder, M. K. 119; 119
Cashman, J. N. *see* Lamond, C. T., (*ESA*) A.204
Castaigne, D. *see* Lequeau, F., (*ESA*) A.97
Castells, C. *see* Fernandez, D., (*ESA*) A.131
Catalá, J. *see* Monedero, P., (*ESA*) A.98
Catalá, J. C., Carrera, J. A., Iribarren, M. J., García Pedrajas, F. and Arroyo, J. L. Effects of diazepam additives on the mononuclear phagocytic system, (*ESA*) A.89
Catalá, J. C. *see* Hidalgo, F., (*ESA*) A.99
Catoire, P., Delaunay, L., Beydon, L., Guerrini, P. and Bonnet, F. Evaluation of systematic TEE in patients suspected of blunt chest trauma, (*ESA*) A.192
Catoire, P. *see* Fulgencio, J. P., (*ESA*) A.42; Liu, N., (*ESA*) A.25
Cattaneo, I., Kayser, V. and Guilbaud, G. Differential effects of specific delta and kappa opioid antagonists on the bidirectionnal effect of naloxone in arthritic rats, (*ESA*) A.114
Cavallier, S. *see* Riou, B., (*ESA*) A.102
Censier, K. *see* Urwyler, A. 76–79
Chabanne, J. P. *see* Descraques, C., (*ESA*) A.127
Chakrabarti, M. K. *see* Wang, C. 63–69
Chambers, W. A. Explaining risk to patients, (*C*) 381–382
Chammas, E. *see* Bromberg, N., (*ESA*) A.28
Chan, K. *see* Jones, R. D. M. 286–292
Chang, C.-L. *see* Tsai, Y.-C. 394–396
Chang, C. S. *see* Jawan, B. 639–641
Chataigneau, T. *see* Le Pelley, E., (*ESA*) A.48
Chatterjee, S. *see* Ravishankar, M., (*C*) 706–707
Chauvin, M., Guirimand, F., Gauneau, P. and Lebrault, C. Effect of morphine on a nociceptive flexion reflex in patients with postoperative pain, (*ESA*) A.115
Chauvin, M. *see* Alfonsi, P., (*ESA*) A.74
Chazalet, J. J. *see* Jacob, L., (*ESA*) A.85
Cheema, S. P. S. *see* Entress, A. H., (*ESA*) A.158
Chennels, P. *see* Murphy, P. G. 583–586
Chong, Z. K. *see* Jawan, B. 639–641
Clacquin, C. *see* Samaha, T., (*ESA*) A.118
Clairoux, M. *see* Katz, J., (*C*) 378
Clarke, B. J. *see* Berrisford, R. G. 201–204
Clarke, F. L. *see* Williams, O. A., (*ARS*) 479P
Clarke, R. S. J. *see* Mirakhur, R. K., (*C*) 235
Clements, F. M. and de Bruijn, N. P., (editors) *Transesophageal Echocardiography*, (*R*) 708
Clergue, F. *see* Annat, G., (*R*) 117; Mouquet, C., (*ESA*) A.83; Nyström, E., (*ESA*) A.65
Cobley, M., Kidd, J. F., Willis, B. A. and Vaughan, R. S. Endobronchial cuff pressures 576–578
Cobley, M. *see* Vaughan, R. S., (*C*) 600
Cody, M. and Johnston, J. Antepartum assessment for anaesthesia, (*C*) 116
Coghlan, S. F. E., McDonald, P. F. and Csepregi, G. Use of alfentanil with propofol for nasotracheal intubation without neuromuscular block 89–91
Cohendy, R. *see* Ripart, J., (*C*) 704
Colardyn, F. *see* De Deyne, C., (*ESA*) A.16; (*ESA*) A.106
Collee, G. G. and Hanson, G. C. The management of acute poisoning 562–573
Collier, C. B. Subdural catheterization and cord damage, (*C*) 384
Collier, C. B., Gatt, S. P. and Lockley, S. M. A continuous subdural block 462–465
Collis, R. *see* Gan, T. J., (*ESA*) A.13
Comte, A. *see* Bazin, J. E., (*ESA*) A.136
Conseiller, C. T. *see* Vassilieff, N., (*ESA*) A.71
Constant, I. *see* Murat, I., (*ESA*) A.165
Contreras, M., (editor) *ABC of Transfusion*, 2nd Edn, (*R*) 495
Cook, T. M. Postoperative pain thresholds, (*C*) 110
Cooney, C. *see* Doyle, M., (*ARS*) 486–487P
Cooper, D. W. and Turner, G. Patient-controlled extradural analgesia to compare bupivacaine, fentanyl and bupivacaine with fentanyl in the treatment of postoperative pain 503–507
Cooper, R., Maddineni, V. R., Mirakhur, R. K. and Wierda, J. M. K. H. Pharmacokinetics of rocuronium (Org 9426) in patients with and without impaired renal function, (*ARS*) 482P
Cooper, R. *see* Maddineni, V. R. 694–695
Cooper, R. A. *see* Mirakhur, R. K., (*C*) 235
Coppo, F. *see* Py, C., (*ESA*) A.57
Coriat, P., Gomez, C., Daas, G., Perel, A. and Viars, P. The systolic pressure variation predicts response to volume loading in patients ventilated after aortic surgery, (*ESA*) A.38
Coriat, P. *see* Beaussier, M., (*ESA*) A.37; Gosgnach, M., (*ESA*) A.5; (*ESA*) A.6; Puybasset, L., (*ESA*) A.39
Cornet, A. *see* Thirion, A.-V., (*ESA*) A.172
Corson, R. J. *see* McKavney, M., (*ARS*) 475P
Cortes, J. *see* Alvarez, J., (*ESA*) A.27
Cortiñas, J. *see* Alvarez, J., (*ESA*) A.27
Cosson, C. *see* Moulay, N., (*ESA*) A.108
Couarraze, G. *see* Benhamou, D., (*ESA*) A.120

Cox, D. J. A. *see* Mallett, S. V., (*C*) 699–700

Cozian, A. *see* Lepage, J. Y., (*ESA*) A.35; Malinovsky, J.-M. 617–620

Cozzone, P. J. *see* Kozak Ribbens, G., (*ESA*) A.92

Craft, T. M. and Upton, P. M., (editors) *Key Topics in Anaesthesia*, (*R*) 117

Crankshaw, D. P. *see* Beemer, G. H., (*C*) 111

Cravalho, E. G. *see* Lee, R. C., (*R*) 601

Crawford, M., Pollock, J., Anderson, K., Glavin, R. J., MacIntyre, D. and Vernon, D. Comparison of midazolam with propofol for sedation in outpatient bronchoscopy 419–422

Crawford, M. E., Molke Jensen, F., Toftdahl, D. B. and Madsen, J. B. Direct spinal effect of intrathecal and extradural midazolam on visceral noxious stimulation in rabbits 642–646

Crea, M. A., Sollazzi, L., Perilli, V., Marana, E. and Ranieri, R. Respiratory effects of laparoscopic cholecystectomy (preliminary data), (*ESA*) A.63

Critchley, J. A. J. H. *see* Critchley, L. A. H. 681–683

Critchley, L. A. H., Critchley, J. A. J. H. and Gin, T. Haemodynamic changes in patients undergoing laparoscopic cholecystectomy: measurement by transthoracic electrical bioimpedance 681–683

Croci, M. *see* Mulazzi, D., (*ESA*) A.54

Cros, A. M. *see* Janvier, G. 186–191

Crozier, T. A., Flamm, C., Speer, C. P., Rath, W., Wuttke, W., Kuhn, W. and Kettler, D. Effects of etomidate on the adrenocortical and metabolic adaptation of the neonate 47–53

Csepregi, G. *see* Coghlan, S. F. E. 89–91

Cunningham, A. *see* McCoy, D., (*ESA*) A.43

Cunningham, A. J., Turner, J., Rosenbaum, S. and Rafferty, T. Transoesophageal echocardiographic assessment of haemodynamic function during laparoscopic cholecystectomy 621–625

Cunningham, A. J. *see* Ryan, T. 101–103

Daas, G. *see* Coriat, P., (*ESA*) A.38

Dahl, J. B. and Kehlet, H. The value of pre-emptive analgesia in the treatment of postoperative pain 434–439

Dahl, J. B., Kehlet, H., Hansen, B. L., Hjortsø, N.-C., Erichsen, C. J. and Møiniche, S. Pre-emptive analgesia, (*C*) 379

Dahlgren, C. *see* Jensen, A. G. 99–100

Dale, O., Frink, E. J., Thommesen, L. and Gandolfi, A. J. Hepatic elimination of diazepam: interactions with albumin, desflurane and sevoflurane 454–455

Dandoy, M. *see* Lampl, E., (*ESA*) A.139

Dapper, F. *see* Boldt, J. 661–665

Davey, A., Moyle, J. T. B. and Ward, C. S. *Ward's Anaesthetic Equipment*, 3rd Edn, (*R*) 240

Davidson, J. A. H. and Gillespie, J. A. Tracheal intubation after induction of anaesthesia with propofol, alfentanil and i.v. lignocaine 163–166

Davidson, T. *see* Phillips, S. 6–9; (*C*) 702–703

Davies, M. J. *see* Murphy, W. G. 205–213

Davies, S. *see* Hanna, M. H. 511–514

Davis, N. R. and Mapleson, W. W. A physiological model for the distribution of injected agents, with special reference to pethidine 248–258; A physiological model for the distribution of injected agents, with special reference to pethidine 711

D'Costa, F. *see* Hanna, M. H. 511–514

Debaene, B., Meistelman, C., Donati, F. and Lienhart, A. Monitoring the onset of neuromuscular blockade at the orbicularis oculi can predict good intubating conditions when using 2 × ED$_{95}$ of atracurium, (*ESA*) A.142

Debaene, B. *see* Plaud, B., (*ESA*) A.141

De Blasio, E. *see* Iannuzzi, E., (*ESA*) A.195

Debord, J. *see* Nathan, N., (*ESA*) A.151

Decoene, C. *see* Bromberg, N., (*ESA*) A.28

Decruyenaere, J. *see* De Deyne, C., (*ESA*) A.16; (*ESA*) A.106

De Deyne, C., Poelaert, J., Decruyenaere, J. and Colardyn, F. Technical aspects of jugular bulb oximetry, (*ESA*) A.16

De Deyne, C., Vandekerckhove, T., Decruyenaere, J., Poelaert, J. and Colardyn, F. Jugular bulb metabolic monitoring during hyperventilation in severe head trauma patients, (*ESA*) A.106

Defrancquen, P. *see* Bardoczky, G. I. 499–502

Degasperi, D., Vinelli, M., Festa, C. and Fiandri, M. T. Hypoxic events after general anaesthesia in the recovery room, (*ESA*) A.59

De Hert, S. G., Gillebert, T. C. and Brutsaert, D. L. Endocardial endothelium modulates *in vivo* left ventricular performance, (*ESA*) A.47

Delaunay, L. *see* Catoire, P., (*ESA*) A.192; Liu, N. 515–518

Delayance, S., Mion, G., Mouren, S., Baron, J.-F., Diaby, M. and Viars, P. Effects of hypertonic saline on coronary blood flow and myocardial performance of a blood-perfused, isolated rabbit heart, (*ESA*) A.45

Delorme, M. *see* Murat, I., (*ESA*) A.166

Delva, E. *see* Camus, Y., (*ESA*) A.72; Lienhart, A., (*ESA*) A.93

Deriaz, H. *see* Duranteau, R., (*ESA*) A.148; Lienhart, A., (*ESA*) A.93

Dernovoi, B. S., Baurain, M. J., d'Hollander, A. A. and Bollen, P. C. Neostigmine antagonism of neuromuscular blockade induced by mivacurium, vecuronium and atracurium, (*ESA*) A.137

Dernovoi, B. S. *see* Baurain, M. J., (*ESA*) A.133; (*ESA*) A.134; (*ESA*) A.135

Desborough, J. P., Jones, P. M., Persaud, S. J. and Howell, S. L. Effects of midazolam on insulin secretion from isolated rat pancreatic islets of Langerhans 221–222; Isoflurane inhibits Ca^{2+}-induced insulin secretion from electrically permeabilised islets of Langerhans, (*ESA*) A.91

Descoins, P. *see* Arné, J., (*ESA*) A.1

Descorps-Déclère, A. *see* Moulay, N., (*ESA*) A.108

Descraques, C., Mion, G., Auroy, Y., Lenoir, B., Pats, B., Rouvier, B. and Chabanne, J. P. Incidence of post dural puncture headache in young adults by the use of the Sprotte needle: 300 patients, (*ESA*) A.127

De Sio, A. *see* Iannuzzi, E., (*ESA*) A.195

Desnault, H. *see* Lienhart, A., (*ESA*) A.93

Despland, P. A. *see* Borgeat, A. 459–461

Devlin, H. B. *see* Lunn, J. N., (*C*) 382

Devlin, J. C. *see* Head-Rapson, A. G., (*ARS*) 487P

De Zen, F. *see* Piccinni, P., (*ESA*) A.78

D'Honneur, G. *see* Liu, N. 515–518

Diaby, M. *see* Delayance, S., (*ESA*) A.45; Fellahi, J. L., (*ESA*) A.44

Diamond, G. *see* Hohner, P., (*ESA*) A.41

Dittmann, M., Schäfer, H.-G., Renkl, F. and Greve, I. Nine years of clinical experience with 29 gauge spinal needles, (*ESA*) A.126

Doenicke, A., Nebauer, A. E., Hoernecke, R., Angster, R. and Mayer, M. Does etomidate cause haemolysis? (*C*) 491

Do-Khac, T. *see* Bodin, L., (*ESA*) A.179

Donati, F. *see* Debaene, B., (*ESA*) A.142

Donnay, M. *see* Legros, F. J., (*ESA*) A.122

Dorkins, H. R. *see* Ball, S. P. 70–75

Dorrance, D. E. *see* Field, L. M. 154–159

Dow, A. C. and Goodman, N. W. Comparison of spontaneous sighs and manual inflations in anaesthetized patients breathing air and oxygen, (*ARS*) 474P; Effect of hyperoxia on the breathing of patients anaesthetized with infusions of propofol 532–535

Dow, A. C. *see* Goodman, N. W. 536–541

Doyle, E., McFadzean, W. and Morton, N. S. I.v. anaesthesia with propofol using a target-controlled infusion system: comparison with inhalation anaesthesia for general surgical procedures in children 542–555

Doyle, M., Mannion, D., McCoy, D., O'Regan, M., Cooney, C. and Fitzpatrick, G. Cardiovascular effects of a pancuronium–vecuronium mixture, (*ARS*) 486–487P

Drewe, J. *see* Urwyler, A. 76–79

Drouet, L. O. *see* Samama, C. M., (*ESA*) A.100

Drummond, G. B. Upper airway reflexes, (*E*) 121–123

Dryden, C. M., McMenemin, I. and Duthie, D. J. R. Efficacy of continuous intercostal bupivacaine for pain relief after thoracotomy 508–510

Dryden, C. M. *see* Smith, D. C., (*C*) 236–237

Dubois, A. *see* Zaouk, G., (*ESA*) A.11

Dubois, M. C. *see* Murat, I., (*ESA*) A.166

Dubousset, A.-M. *see* Jamali, S., (*ESA*) A.160

Dubray, C. *see* Bazin, J. E., (*ESA*) A.136

Dupont, H., Nyarwaya, J.-B. and Samii, K. A comparison of midazolam and midazolam plus fentanyl for colonoscopy, (*ESA*) A.9

Dupuis, J. L. *see* Nathan, N., (*ESA*) A.151

Durak, P., Özgök, A., Esen, H., Erdemli, Ö. and Ebil, S. The combined prophylactic administration of H1 and H2 receptor blockers in the prevention of protamine related haemodynamic effects and the relation between antihistaminics-leucocytes and pulmonary vascular resistance, (*ESA*) A.95

Durak, P., Özgök, A., Saydam, G., Türkmen, A., Erdemli, Ö. and Ebil, S. The relationship between cardiopulmonary bypass related immunologic effects and complement, thromboxane and leucocyte parameters, (*ESA*) A.96

Duranteau, R., Guesde, R., Riou, B., Deriaz, H. and

Viars, P. Computer-controlled syringe pump improves safety of pharmacokinetic models, (*ESA*) A.148
Duranteau, R. *see* Riou, B., (*ESA*) A.80
Durbec, O. *see* Albanese, J., (*ESA*) A.107
Duthie, D. J. R. *see* Dryden, C. M. 508–510
Dwyer, R. *see* McCoy, D., (*ESA*) A.43
Dzoljic, M., Geller, E., Rupreht, J., Erdmann, W. and Dzoljic, M. R. Nitrous oxide induced neuronal depression: modification through benzodiazepine receptors, (*ESA*) A.112
Dzoljic, M. R. *see* Dzoljic, M., (*ESA*) A.112

Eberhard, A. *see* Py, C., (*ESA*) A.57
Ebil, S. *see* Durak, P., (*ESA*) A.95; (*ESA*) A.96
Ecoffey, C. *see* Auroy, Y., (*ESA*) A.76; Jamali, S., (*ESA*) A.160; Mahé, V., (*ESA*) A.109; Meistelman, C., (*ESA*) A.138; Moulay, N., (*ESA*) A.108; Nègre, I., (*ESA*) A.203; Orliaguet, G., (*ESA*) A.163; Reignier, J., (*ESA*) A.162; Samaha, T., (*ESA*) A.118
Eddleston, J. M. Intermittent *vs* continuous extradural infusion of bupivacaine during labour, (*C*) 490
Edgren, J. *see* Pere, P. 276–279
Edouard, A. *see* Mimoz, O., (*ESA*) A.180
Eduardo, A. *see* Murphy, W. G. 205–213
Edwards, J. *see* Wolf, A. R. 654–660
Edwards, M. B. *see* Goodman, N., (*R*) 385
Edwards, W. T. *see* Ready, L. B., (*R*) 495
Eftedal, O. *see* Flook, V., (*ARS*) 474–475P
Ehrenström Reiz, G. *see* Nath, S., (*ESA*) A.211
Eintrei, C. *see* Jensen, A. G. 99–100
Ejlersen, E., Jensen, M. B. and Eliasen, K. Outcome for patients in intensive care with acute renal failure requiring dialysis, (*ESA*) A.7
Eldar, I. *see* Preisman, S., (*ESA*) A.124
Eledjam, J. J. *see* de la Coussaye, J. E., (*ESA*) A.121; Lefrant, J. Y., (*ESA*) A.18
Eledjam, J.-J. *see* Ripart, J., (*C*) 704
Eleftheriadis, S., Kuppe, H., Klotz, K.-F. and Schmucker, P. Anesthesia for patients ⩾ 90 years of age in emergency hip surgery, (*ESA*) A.3
Eleftheriadis, S. *see* Kuppe, H., (*ESA*) A.31
Elhaddoury, M. *see* Hamza, J., (*ESA*) A.171
Eliasen, K. *see* Ejlersen, E., (*ESA*) A.7
Elliott, R. H. and Strunin, L. Hepatotoxicity of volatile anaesthetics 339–348
Ellis, F. R., Halsall, P. J. and Hopkins, P. M. Combined caffeine–halothane test for malignant hyperthermia, (*C*) 598
Ellis, F. R. *see* Ball, S. P. 70–75; Halsall, P. J., (*C*) 599; Hopkins, P. M. 397–401
Ellison, W. *see* Janvier, G. 186–191
Engberg, G. *see* Rothen, H. U., (*ESA*) A.53
Engbers, F. *see* Boer, F., (*ESA*) A.147
Engelman, E., Bardoczky, G. and d'Hollander, A. Influence of posture on the respiratory mechanics during anesthesia, (*ESA*) A.56
Engelman, E. and Lipszyc, M. Effects of oral preoperative guanfacine on anesthetics requirements, (*ESA*) A.144
Engelman, E. *see* Bardoczky, G., (*ESA*) A.55; Bardoczky, G. I. 499–502
England, R. E. *see* Watt, T., (*ARS*) 477P
Englesson, S. *see* Karlsten, R. 411–413
Entress, A. H. and Cheema, S. P. S. Use of thoracic epidural block for perioperative analgesia in children, (*ESA*) A.158
Erdemli, Ö. *see* Durak, P., (*ESA*) A.95; (*ESA*) A.96
Erdmann, W. *see* Dzoljic, M., (*ESA*) A.112
Erichsen, C. J. *see* Dahl, J. B., (*C*) 379
Ernst, E. *see* Morris, R. W., (*ESA*) A.2
Erskine, R. J., Murphy, P. J. and Langton, J. A. Effect of stopping smoking on upper airway reflexes, (*ARS*) 478P
Erskine, R. J., Murphy, P. J., Langton, J. A. and Smith, G. Effect of age on the sensitivity of upper airway reflexes 574–575
Esen, H. *see* Durak, P., (*ESA*) A.95
Espadaler, J. M. *see* Fernandez, S., (*ESA*) A.119
Eurin, B. *see* Jacob, L., (*ESA*) A.85
Evans, R. *see* Palazzo, M. 135–140
Eyres, R. L. *see* Wolf, A. R. 654–660

Fale, A. D. *see* Freeman, S. J. 226–227
Faragher, B. *see* Watt, T., (*ARS*) 477P
Fargnoli, J. M. *see* Py, C., (*ESA*) A.57
Farhat, F. *see* Spencer, A., (*ESA*) A.207
Faris, P. P., Ritter, M., Abels, R. and Gordon, D. Effects of recombinant-human erythropoietin on postoperative transfusion requirements in subjects undergoing major orthopaedic surgery, (*ESA*) A.101
Faucon, G. *see* Freysz, M., (*ESA*) A.46
Fawcett, W. J. *see* Ooi, R. 17–21; 494
Feiss, P. *see* Nathan, N., (*ESA*) A.151
Feldman, S. A. *see* Campkin, N. T. A. 581–582; Hood, J. R., (*ARS*) 480P; Law Min, J.-C., (*ARS*) 480–481P
Fell, D. Postoperative analgesia in children, (*E*) 4–5
Fellahi, J. L., Ouardali, F., Mouren, S., Baron, J.-F., Diaby, M. and Viars, P. Functional recovery after 24 h preservation of rabbit hearts in University Wisconsin solution, (*ESA*) A.44
Felletter, P., Breschinski, W. and Bock, K. H. Helicopter transportation of patients with symptomatic aortic aneurysms, (*ESA*) A.196
Ferguson, C. *see* Nathanson, M. H., (*ARS*) 481–482P
Fernandez, D., Castells, C., Rue, M., Bernaus, M. and Puig, M. M. Subarachnoid anaesthesia (SAA) and postoperative analgesia with bupivacaine (BV) plus fentanyl (FN) in geriatric patients, (*ESA*) A.131
Fernandez, S., Monells, J., Espadaler, J. M. and Puig, M. M. Effects of intrathecal meperidine (MP), fentanyl (FN) and lidocaine (LD) on somatosensory (SSEP) and cortical motor (CMEP) evoked potentials in humans, (*ESA*) A.119
Ferraro, F. *see* Iannuzzi, E., (*ESA*) A.195
Festa, C. *see* Degasperi, D., (*ESA*) A.59
Fiandri, M. T. *see* Degasperi, D., (*ESA*) A.59
Field, L. M., Dorrance, D. E., Krzeminska, E. K. and Barsoum, L. Z. Effect of nitrous oxide on cerebral blood flow in normal humans 154–159
Findley, I. L. *see* Bailey, C. R., (*ESA*) A.169
Fiset, P. *see* Meistelman, C., (*ESA*) A.138
Fisher, D. M. Pharmacokinetic/pharmacodynamic modelling of atracurium, (*C*) 110–111
Fitzpatrick, G. *see* Doyle, M., (*ARS*) 486–487P
Flamm, C. *see* Crozier, T. A. 47–53
Fleischer, F. *see* Rauch, H., (*ESA*) A.30
Fleron, M.-H. *see* Gosgnach, M., (*ESA*) A.5
Flook, V. Asymmetry of uptake and washout of inert gases—lessons learnt in an anaesthetic department, (*ARS*) 487–488P
Flook, V., Eftedal, O. and Brubakk, A. O. Hyperbaric decompression bubble formation—building on the Mapleson model of gas dynamics, (*ARS*) 474–475P
Flynn, P. J. *see* Palayiwa, E., (*ARS*) 485P
Foëx, P. *see* Reeder, M. K. 119; 119
Fogas, J. *see* Vereczkey, Z., (*ESA*) A.64
Foppoli, R., Lunghi, P., Bonara, Z., Mora, C. and Stacca, R. Fentanyl or buprenorphine side effects in spinal anaesthesia, (*ESA*) A.132
Forbes, D., Binning, A. and Scott, N. B. The effect of parenteral diclofenac and morphine on efficacy duration and height of blockade during continuous epidural bupivacaine 0.5%, (*ESA*) A.125
Fox, D. Bacterial retention properties of heat and moisture exchange filters, (*C*) 382
François, G. *see* Viviand, X., (*ESA*) A.150
Frankenberg, C. *see* Kulka, P. J., (*ESA*) A.143
Franklin, K. *see* Bålfors, E., (*ESA*) A.62
Freeman, S. J. and Fale, A. D. Muscular paralysis and ventilatory failure caused by hyperkalaemia 226–227
Freysz, M., Timour, Q., Bertrix, L., Loufoua, J. and Faucon, G. Pre- and intraoperative prevention by β-blockers, propranolol and esmolol, of ischaemia-induced ventricular fibrillation, (*ESA*) A.46
Friedman, A. *see* Hohner, P., (*ESA*) A.41
Frink, E. J. *see* Dale, O. 454–455
Frossard, J. *see* Meistelman, C., (*ESA*) A.138
Fruhstorfer, H. and Wagener, G. Effects of intradermal lignocaine and mepivacaine on human cutaneous circulation in areas with histamine-induced neurogenic inflammation 167–172
Fulgencio, J. P., Rimaniol, J. M., Saada, M., Catoire, P. and Bonnet, F. Epidural clonidine and myocardial ischaemia after abdominal aortic surgery, (*ESA*) A.42
Fung, C. *see* Hanna, M. H. 511–514
Fusciardi, J. *see* Arné, J., (*ESA*) A.1; Lacoste, L., (*ESA*) A.66; (*ESA*) A.67; Le Pelley, E., (*ESA*) A.48
Fyhrquist, F. *see* Kuitunen, A. 173–180

Gajraj, N. M. *see* Van Elstraete, A. C. 691–693
Gallart, L. L. *see* Samsó, E., (*ESA*) A.205
Gan, T. J., Collis, R. and Hetreed, M. Double-blind comparison of ondansetron, droperidol and saline for prevention of nausea & vomiting after orthopaedic surgery, (*ESA*) A.13
Gandolfi, A. J. *see* Dale, O. 454–455

Gannedahl, P. *see* Odeberg, S., (*ESA*) A.34
García Pedrajas, F. *see* Catalá, J. C., (*ESA*) A.89
García-Pedrajas, F. *see* de los Ríos, J., (*ESA*) A.75
Garrec, F. *see* Lepage, J. Y., (*ESA*) A.35
Gatt, S. P. *see* Collier, C. B. 462–465
Gauneau, P. *see* Chauvin, M., (*ESA*) A.115
Gauss, A., Treiber, H. S., Haehnel, J. and Johannsen, H. S. Spontaneous reposition of a dislocated arytenoid cartilage 591–592
Gehring, H. *see* Kuppe, H., (*ESA*) A.31
Geiger, C., Kick, O., Böhrer, H., Motsch, J. and Martin, E. Comparison of ondansetron, metoclopramide and droperidol for the prophylaxis of emetic symptoms after gynecological laparoscopic procedures, (*ESA*) A.14
Geißler, C. *see* Schregel, W., (*ESA*) A.105
Geisslinger, G., Hering, W., Thomann, P., Knoll, R., Kamp, H.-D. and Brune, K. Pharmacokinetics and pharmacodynamics of ketamine enantiomers in surgical patients using a stereoselective analytical method 666–671
Geller, E. *see* Dzoljic, M., (*ESA*) A.112
Gentili, M. E. and Wargnier, J. P. Peripheral nerve damage and regional anaesthesia, (*C*) 594
Georgiou, L., Vourlioti, A., Kremastinou, F., Stefanou, P. and Tsiotou, A. Influence of anaesthesia on postoperative hypoxaemia, (*ESA*) A.60
Gérard, P. *see* Bermejo, N. 322–325
Gerling, W. *see* Kuppe, H., (*ESA*) A.31; Schäfer, R., (*ESA*) A.184
Gibson, J. S. *see* Murphy, P. G. 583–586
Giebler, R. M. *see* Scherer, R. U. 689–690
Giesecke, A. H. *see* Sharkey, A. 449–450
Gilbart, E. *see* Zaouk, G., (*ESA*) A.11
Gillart, T. *see* Bazin, J. E., (*ESA*) A.136
Gillebert, T. C. *see* De Hert, S. G., (*ESA*) A.47
Gillespie, J. A. *see* Davidson, J. A. H. 163–166
Gilligan, S., Smith, M. B. and Allen, P. R. Transthoracic endoscopic sympathectomy, (*C*) 491
Gillon, M.-C. *see* Auroy, Y., (*ESA*) A.76
Gilly, H. *see* Weindlmayr-Goettel, M. 579–580
Gin, T., O'Meara, M. E., Kan, A. F., Leung, R. K. W., Tan, P. and Yau, G. Plasma catecholamines and neonatal condition after induction of anaesthesia with propofol or thiopentone at Caesarean section 311–316
Gin, T. *see* Critchley, L. A. H. 681–683
Ginsburg, R. *see* Lippmann, M., (*C*) 235
Giron, G. P. *see* Armellin, G., (*ESA*) A.104; Marcassa, A., (*ESA*) A.168
Glavin, R. J. *see* Crawford, M. 419–422
Goarin, J. P., Le Bret, F., Jacquens, Y., Riou, B., Saada, M. and Viars, P. Diagnosis of aortic rupture by transesophageal echocardiography (TEE), (*ESA*) A.193
Goarin, J.-P. *see* Saada, M., (*ESA*) A.194; Vivien, B., (*ESA*) A.183
Goddard, J. M. Nitrous oxide administration via oxygen therapy devices, (*C*) 238
Goldhill, D. R. *see* Nolan, K. M. 440–442
Goldman, M. D. *see* Reeder, M. K. 119; 119; 119
Gomez, C. *see* Coriat, P., (*ESA*) A.38
Goodman, N. and Edwards, M. B., (editors) *Medical Writing: A Prescription for Clarity*, (*R*) 385
Goodman, N. W. Different rates of injection of propofol, (*C*) 383
Goodman, N. W. and Dow, A. C. Effects of active and passive sighs in normoxia and hyperoxia on the breathing of patients anaesthetized with infusions of propofol 536–541
Goodman, N. W. *see* Dow, A. C., (*ARS*) 474P; 532–535; Michel, M. Z., (*R*) 709
Goodnough, L. T. The role of recombinant growth factors in transfusion medicine 80–86
Goodwin, A. P. L. *see* Walker, M. B., (*C*) 114
Gordon, D. *see* Faris, P. P., (*ESA*) A.101
Gosgnach, M., Bertrand, M., Pironkov, A., Coriat, P. and Viars, P. Does routine preoperative coronary angiography modify outcome after aortic surgery? (*ESA*) A.6
Gosgnach, M., Coriat, P., Fleron, M.-H., Bertrand, M. and Viars, P. Indications for coronary revascularisation in vascular surgical patients, (*ESA*) A.5
Gosgnach, M., Le Bret, F., Smail, N., Beaussier, M. and Viars, P. Tolerance of preoperative transesophageal echocardiography in patients scheduled for aortic surgery, (*ESA*) A.21
Gosgnach, M. *see* Beaussier, M., (*ESA*) A.37; Puybasset, L., (*ESA*) A.39
Goudsouzian, N. G. *see* Shorten, G. D. 160–162
Gouin, F. *see* Martin, C., (*ESA*) A.20; (*ESA*) A.189; (*ESA*) A.190
Graham, S. *see* Appadu, B., (*ARS*) 477P
Graham-Smith, D. G. and Aronson, J. K. *The Oxford Textbook of Clinical Pharmacology and Drug Therapy*, 2nd Edn, (*R*) 601
Granry, J. C., Monrigal, C., Jacob, J. P. and Monrigal, J. P. Cerebral blood flow velocities (CBFV) during anaesthesia for gynaecological laparoscopic surgery, (*ESA*) A.32
Gray, P. A. *see* Polster, M. R. 612–616
Greaves, D. J. *see* Morris, R. W., (*ESA*) A.2
Green, C. J. *see* Campbell, I. T., (*C*) 236
Green, D. W., O'Connor, L. and Hanna, M. Efficacy of postoperative pain treatment regimens using both buprenorphine and papaveretum sequentially after abdominal hysterectomy 626–630
Green, T. *see* Bennett, S., (*ESA*) A.152
Greenstein, D. *see* Gupta, N. K., (*C*) 699
Greve, I. *see* Dittmann, M., (*ESA*) A.126
Griffin, R. M. *see* Stevens, J. J. W. M. 107–109
Griffiths, A. G., Beards, S. C., Jackson, A. and Horsman, E. L. Visualization of extradural blood patch for post lumbar puncture headache by magnetic resonance imaging 223–225
Griffiths, R. *see* Appadu, B., (*ARS*) 477P
Grint, E. *see* Palayiwa, E., (*ARS*) 485P
Grond, S. *see* Radbruch, L., (*ESA*) A.212
Guéant, J. L. *see* Bermejo, N. 322–325
Guéneron, J. P. *see* Nègre, I., (*ESA*) A.203
Guerrero, M. *see* Riou, B., (*ESA*) A.103
Guerrini, P. *see* Catoire, P., (*ESA*) A.192
Guesde, R., Ourahma, S., Riou, B. and Viars, P. Effects of desmopressin (DDAVP) supplementation in brain dead organ donors (BDOD) on early recipient renal function, (*ESA*) A.79
Guesde, R. *see* Duranteau, R., (*ESA*) A.148; Riou, B., (*ESA*) A.80
Guidon-Attali, C. *see* Viviand, X., (*ESA*) A.150
Guilbaud, G. *see* Cattaneo, I., (*ESA*) A.114
Guirimand, F., Strimbu, M., Willer, J. C. and Le Bars, D. Involvement of μ, δ, and κ receptors in the inhibition by intrathecal morphine of a C-fibre evoked reflex in the rat, (*ESA*) A.116
Guirimand, F. *see* Chauvin, M., (*ESA*) A.115
Gulden, R. H. *see* Sharkey, A. 449–450
Günnicker, F. M. *see* Scherer, R. U. 689–690
Gupta, N. K., Martin, P. G., Greenstein, D. and Walker, D. R. Haemostasis and thrombelastography: a cautious note, (*C*) 699
Guy, J. G. *see* Jones, N. O., (*C*) 235–236
Güzeldemir, M. E. *see* Bayhan, N., (*ESA*) A.123

Haehnel, J. *see* Gauss, A. 591–592
Häggmark, S. *see* Hohner, P., (*ESA*) A.23; (*ESA*) A.26; (*ESA*) A.41; Reiz, S., (*ESA*) A.24; (*ESA*) A.52
Hak, A. *see* Boer, F., (*ESA*) A.147
Hall, J. L. *see* Ball, S. P. 70–75
Hallén, J. *see* Rawal, N. 280–285
Halliday, D. *see* Carli, F., (*ESA*) A.86
Halsall, P. J., Ellis, F. R. and Knowles, P. F. Spin resonance spectroscopy to detect malignant hyperthermia susceptibility, (*C*) 599
Halsall, P. J. *see* Ball, S. P. 70–75; Ellis, F. R., (*C*) 598; Hopkins, P. M. 397–401
Hamdi, A. *see* Berrisford, R. G. 201–204
Hamilton-Davies, C. *see* Mythen, M., (*ESA*) A.29
Hammermann, H. *see* Boldt, J. 661–665
Hamunen, K. Ventilatory effects of morphine, pethidine and methadone in children 414–418
Hamza, J., Narchi, P., Elhaddoury, M. and Benhamou, D. Adequate pain relief with epidural analgesia during labor: why are women still dissatisified? (*ESA*) A.171
Hamza, J. *see* Menigaux, C., (*ESA*) A.175
Hanbury, A. *see* McKavney, M., (*ARS*) 475P
Hanna, M. *see* Green, D. W. 626–630
Hanna, M. H., D'Costa, F., Peat, S. J., Fung, C., Venkat, N., Zilkha, T. R. and Davies, S. Morphine-6-glucuronide disposition in renal impairment 511–514
Hannemann, L. *see* Meier-Hellmann, A., (*ESA*) A.185; Spies, C., (*ESA*) A.186
Hansen, B. L. *see* Dahl, J. B., (*C*) 379
Hanson, G. C. *see* Collee, G. G. 562–573
Harden, R. M. *see* Arnold, C. 118
Hardy, P. A. J. Pre-emptive extradural analgesia, (*C*) 493
Harf, A. *see* Beydon, L., (*ESA*) A.4
Hargreaves, J. Metal particle generation caused by the combined spinal–extradural technique, (*C*) 706
Harris, R. W. *see* Williams, O. A., (*ARS*) 479P
Harrison, D. A. *see* Langham, B. T. 519–521
Harvey, A. L. *see* Braga, M. F. M. 405–410
Hasan, M. A., Thomas, T. A. and Prys-Roberts, C.

Comparison of automatic oscillometric arterial pressure measurement with conventional auscultatory measurement in the labour ward 141–144

Hatfield, A. and Tronson, M. *The Complete Recovery Room Book*, (*R*) 709

Hausdörfer, J. *see* Strauß, J. M. 363–364

Haußmann, R. *see* Rauch, H., (*ESA*) A.30

Hawelski, T. *see* Pasch, T., (*ESA*) A.153

Head-Rapson, A. G., Devlin, J. C., Lovell, G. G., Parker, C. J. R. and Hunter, J. M. Pharmacokinetics of the isomers of mivacurium chloride in the healthy adult, (*ARS*) 487P

Head-Rapson, A. G. and Snowdon, S. L. Routine preoxygenation: how long before mask anaesthesia? (*ARS*) 488P

Healy, T. E. J. *see* Barrie, J. R. 468–470; Beatty, P. C. W., (*C*) 707

Heath, M. L. and Allagain, J. Cricoid pressure and the laryngeal mask airway, (*C*) 596

Heckletsweiler, B. *see* Moritz, F. 451–453

Hedenstierna, G. *see* Rothen, H. U., (*ESA*) A.53

Heil, T., Spies, C., Neumann, T. and Müller, C. Carbohydrate deficient transferrin: a new copredictor of alcoholism related postoperative complications? (*ESA*) A.88

Heil, T. *see* Spies, C., (*ESA*) A.110

Heiss-Dunlop, W. *see* Meier-Hellmann, A., (*ESA*) A.185

Hellstrand, P. *see* Rawal, N. 280–285

Hempelmann, G. *see* Boldt, J. 661–665

Henderson, P. D. *see* Berthoud, M. C. 423–427

Hennart, D. and Mersch, Y. Analgesia by wound infiltration before or after surgery in inguinal herniorrhaphy, (*ESA*) A.202

Hennessy, N., Mahajan, R. P. and Aitkenhead, A. R. Effect of three different surgical prone positions on lung volumes in healthy, awake volunteers, (*ARS*) 475P

Hennessy, N. *see* Mahajan, R. P., (*ARS*) 482–483P

Henry, M. *see* Thirion, A.-V., (*ESA*) A.172; Thormann, F., (*ESA*) A.173

Hering, W. *see* Geisslinger, G. 666–671

Hetreed, M. *see* Gan, T. J., (*ESA*) A.13

Hewlett, A. M. *see* Landon, A. J. 605–611

Heytens, L. and Boosaert, L. Prolonged (> 1 week) sedation with midazolam in ICU patients: efficacy, safety and pharmacokinetics, (*ESA*) A.178

Hickman, J. *see* Tolley, P., (*C*) 115

Hidalgo, F., Páramo, J. A., Catalá, J. C., Carrascosa, F. and Monedero, P. High dose aprotinin *versus* desmopressin acetate treatment in cardiac surgery, (*ESA*) A.99

Hirst, R. A. and Lambert, D. G. Halothane enhances forskolin stimulated cyclic adenosine-3′,5′-monophosphate formation in human neuroblastoma cells, (*ARS*) 486P

Hirst, R. A. *see* Lambert, D. G., (*ARS*) 475–476P

Hjortsø, N.-C. *see* Dahl, J. B., (*C*) 379

Hoernecke, R. *see* Doenicke, A., (*C*) 491

Hohner, P., Backman, C., Diamond, G., Friedman, A., Häggmark, S., Johansson, G., Karp, K. and Reiz, S. Effects of nitrous oxide (N_2O) on systemic haemodynamics, regional left ventricular (LV) function and incidence of myocardial ischaemia (MI) in vascular surgical patients with coronary artery disease (CAD), (*ESA*) A.41

Hohner, P., Johansson, G., Häggmark, S., Mehta, V. and Reiz, S. Evaluation of haemodynamic indices of myocardial ischaemia in patients with coronary artery disease (CAD), (*ESA*) A.23

Hohner, P., Mehta, V., Saada, M., Häggmark, S., Jansson, E., Johansson, G. and Reiz, S. Sensitivity and specificity of mechanical and electrocardiographic myocardial ischaemia (MI) monitoring techniques, (*ESA*) A.26

Hohner, P. *see* Reiz, S., (*ESA*) A.24

Hoile, R. W. *see* Lunn, J. N., (*C*) 382

Holcroft, J. *see* Jacobson, W. 522–526

Holdcroft, A. *see* Wang, C. 63–69

d'Hollander, A. *see* Bardoczky, G., (*ESA*) A.55; Engelman, E., (*ESA*) A.56

d'Hollander, A. A. *see* Baurain, M. J., (*ESA*) A.133; (*ESA*) A.134; (*ESA*) A.135; Dernovoi, B. S., (*ESA*) A.137

Hollway, T. E. *see* Phillips, S. 687–688

Holst-Larsen, H. *see* Søreide, E. 360–362

Holtby, H. M. *see* Alderson, P. J. 145–148

Hongnat, J.-M. *see* Alfonsi, P., (*ESA*) A.74

Hood, J. R., Campkin, N. and Feldman, S. A. Comparison of the onset of depolarizing *vs* non-depolarizing block after early tourniquet release in the isolated forearm, (*ARS*) 480P

Hood, J. R. *see* Campkin, N. T. A. 581–582; Law Min, J.-C., (*ARS*) 480–481P

Hopkins, P. M., Ellis, F. R. and Halsall, P. J. Comparison of *in vitro* contracture testing with ryanodine, halothane and caffeine in malignant hyperthermia and other neuromuscular disorders 397–401

Hopkins, P. M. *see* Ball, S. P. 70–75; Ellis, F. R., (*C*) 598

Horsman, E. L. *see* Griffiths, A. G. 223–225

Howell, S. L. *see* Desborough, J. P., (*ESA*) A.91; 221–222

Huang, Y. F., Upton, R. N. and Runciman, W. B. I.v. bolus administration of subconvulsive doses of lignocaine to conscious sheep: myocardial pharmacokinetics 326–332; I.v. bolus administration of subconvulsive doses of lignocaine to conscious sheep: relationships between myocardial pharmacokinetics and pharmacodynamics 556–561

Huang, Y. F. *see* Upton, R. N. 333–338

Hughes, D. *see* Wolf, A. R. 10–16

Hume, M. A. *see* Smith, D. C., (*C*) 236–237

Hunter, J. M. and Shearer, E. S. Mortality in ITU patients receiving neuromuscular blocking drugs, (*C*) 238–239

Hunter, J. M. *see* Head-Rapson, A. G., (*ARS*) 487P; Parker, C. J. R. 38–41; (*C*) 111–112; 443–445

Hurson, B. J. *see* Joshi, G. P. 87–88

Hutchinson, S. *see* Phillips, S. 6–9; (*C*) 702–703

Hutchinson, S. E. *see* Phillips, S. 687–688

Hynynen, M. *see* Kuitunen, A. 173–180

Iannuzzi, E., De Blasio, E., Ferraro, F., De Sio, A. and Schiraldi, F. The choice of ECM rate could improve the neuroprotection during CPR, (*ESA*) A.195

Ikeda, K. *see* Nakajima, R. 273–275

Inglis, T. J. J. Evidence for dynamic phenomena in residual tracheal tube biofilm 22–24

Inglis, T. J. J., Jones, J. G. and Paxton, S. Penetration of an aerosol, produced by film atomization, through the carinal bifurcation 527–531

Ingrand, P. *see* Lacoste, L., (*ESA*) A.66

Innes, P., Allsop, E., Lockie, J., Kirton, C. and Booker, P. Comparison of dobutamine with enoximone following open heart surgery in small children, (*ESA*) A.167

Iribarren, M. J. *see* Carrera, J., (*ESA*) A.77; Catalá, J. C., (*ESA*) A.89; de los Ríos, J., (*ESA*) A.75

Ivens, D. and Verborgh, C. Is correlation of arterial and end-tidal carbon dioxide pressure during inhalation anaesthesia better with laryngeal mask as compared to face mask? (*ESA*) A.17

Jackson, A. *see* Griffiths, A. G. 223–225

Jackson, R. *see* Murphy, P. G. 583–586

Jacob, J. P. *see* Granry, J. C., (*ESA*) A.32

Jacob, L., Chazalet, J. J., Payen, D., Bedrossian, J., Teillac, P. and Eurin, B. Renal blood flow and function relationship in recent renal transplantation in man, (*ESA*) A.85

Jacobs, D. *see* Zaouk, G., (*ESA*) A.11

Jacobson, W., Park, G. R., Saich, T. and Holcroft, J. Surfactant and adult respiratory distress syndrome 522–526

Jacquens, Y. *see* Goarin, J. P., (*ESA*) A.193; Riou, B., (*ESA*) A.80; Saada, M., (*ESA*) A.194

Jakeways, M. S. R. and Carli, F. Laparoscopic *vs* open cholecystectomy, (*C*) 597

Jalkanen, L. *see* Meretoja, O. A., (*ESA*) A.140

Jamali, S., Monin, S., Begon, C., Dubousset, A.-M. and Ecoffey, C. Clonidine in paediatric caudal anaesthesia, (*ESA*) A.160

Jamali, S. *see* Nègre, I., (*ESA*) A.203

Jansson, E. *see* Hohner, P., (*ESA*) A.26; Nyström, E., (*ESA*) A.65

Jäntti, V. *see* Yli-Hankala, A. 54–57

Janvier, G., Bordenave, L., Revel, P., Ellison, W., Cros, A. M. and Winnock, S. Mathematical analysis of the upper respiratory tract from an anthropometric study 186–191

Järvinen, A. *see* Kuitunen, A. 173–180

Jawan, B., Lee, J. H., Chong, Z. K. and Chang, C. S. Spread of spinal anaesthesia for Caesarean section in singleton and twin pregnancies 639–641

Jayr, C. *see* Spencer, A., (*ESA*) A.207

Jedeiken, R., Olsfanger, D., Shachor, D. and Mansoor, K. Transthoracic endoscopic sympathectomy, (*C*) 491–492

Jensen, A. G., Dahlgren, C. and Eintrei, C. Propofol decreases random and chemotactic stimulated locomotion of human neutrophils *in vitro* 99–100

Jensen, M. B. *see* Ejlersen, E., (*ESA*) A.7

Jessop, J. and Jones, J. G. Effect of nitrous oxide on auditory evoked potentials, (*C*) 380

Johannsen, H. S. *see* Gauss, A. 591–592

Johansson, G. *see* Hohner, P., (*ESA*) A.23; (*ESA*) A.26; (*ESA*) A.41; Österlund, B., (*ESA*) A.19; Reiz, S., (*ESA*) A.24; (*ESA*) A.52; Svanström, M., (*ESA*) A.177
Johnson, A. *see* Attebo, L. 372–377
Johnston, J. *see* Cody, M., (*C*) 116
Joly, L.-M. and Benhamou, D. Continuous monitoring of Sp_{O_2} during total intravenous anaesthesia with ketamine and spontaneous ventilation, (*ESA*) A.58
Jones, J. G. *see* Inglis, T. J. J. 527–531; Jessop, J., (*C*) 380; Munglani, R., (*ARS*) 483–484P
Jones, N. O. and Guy, J. G. Blood loss during total hip replacement, (*C*) 235–236
Jones, P. M. *see* Desborough, J. P., (*ESA*) A.91; 221–222
Jones, R. D. M., Chan, K., Roulson, C. J., Brown, A. G., Smith, I. D. and Mya, G. H. Pharmacokinetics of flumazenil and midazolam 286–292
Jones, R. M. *see* Munday, I. T., (*ARS*) 480P; Watson, N. A., (*ARS*) 479P
de Jong, J. R., Ros, H. H. and de Lange, J. J. Clinical evaluation of the calibration of noninvasive continuous blood pressure measurement devices by means of oscillometric blood pressure measurements, (*ESA*) A.15
Joos, S., Quintilla, R. and Servais, R. Sequential spinal peridural anaesthesia for gynaecological surgery under laparoscopy, (*ESA*) A.130
Jordan, M. J. *see* Nathanson, M. H., (*ARS*) 481–482P
Joris, J. Metabolic effects of cholecystectomy, (*C*) 494
Joris, J. and Lamy, M. Neuroendocrine changes during pneumoperitoneum for laparoscopic cholecystectomy, (*ESA*) A.33
Joshi, G. P. Pain relief after anterior cruciate ligament repair, (*C*) 600
Joshi, G. P., McCarroll, S. M., Brady, O. H., Hurson, B. J. and Walsh, G. Intra-articular morphine for pain relief after anterior cruciate ligament repair 87–88
Joshi, P. and Ooi, R. Nitrous oxide administration via oxygen therapy devices, (*C*) 238
Joyce, C. *see* Baker, A. B. 259–266

Kaddour, C. *see* Bodin, L., (*ESA*) A.191
Kaeffer, N. *see* Moritz, F. 451–453
Kalfon, P., Rouby, J. J. and Viars, P. Comparison of pressure support ventilation provided by two ICU ventilators, (*ESA*) A.182
Kalfon, P. *see* Beaussier, M., (*ESA*) A.37
Kalli, I. Effect of isometric thumb preload on the evoked compound muscle action potential 92–93
Kamp, H.-D. *see* Geisslinger, G. 666–671
Kan, A. F. *see* Gin, T. 311–316
Kanayama, T. *see* Takada, K. 181–185
Kanto, J. *see* Ali-Melkkilä, T., (*ESA*) A.145
Karalazos, L. *see* Skourtis, C., (*ESA*) A.36
Karayan, J. *see* Lacoste, L., (*ESA*) A.66; (*ESA*) A.67
Karling, M. A national database for intensive care medicine in Sweden, (*ESA*) A.8
Karling, M. *see* Östman, M., (*ESA*) A.22
Karlsten, R. and Englesson, S. An alternative method of increasing P_{CO_2} using apnoea and continuous positive airway pressure 411–413
Karp, K. *see* Hohner, P., (*ESA*) A.41; Östman, M., (*ESA*) A.22
Katz, J., Kavanagh, B. P., Clairoux, M. and Sandler, A. N. Pre-emptive analgesia, (*C*) 378
Kaufman, L., (editor) *Anaesthesia Review 9*, (*R*) 385
Kaufmann, M. A. *see* Urwyler, A. 76–79
Kaukinen, L. *see* Ojanen, R., (*ESA*) A.94
Kaukinen, S. *see* Ojanen, R., (*ESA*) A.94
Kavanagh, B. P. *see* Katz, J., (*C*) 378
Kay, P. H., (editor) *Techniques in Extracorporeal Circulation*, 3rd Edn, (*R*) 239–240
Kayser, V. *see* Cattaneo, I., (*ESA*) A.114
Keegan, M. *see* McKavney, M., (*ARS*) 475P
Kehlet, H. *see* Dahl, J. B., (*C*) 379; 434–439
Kendig, J. *see* Salonen, M., (*ESA*) A.113
Kenna, J. G. and Knight, T. L. Halothane, metabolite-induced antibodies and hepatotoxicity, (*ARS*) 484–485P
Kenny, G. N. C. *see* Pollock, J. S. S. 219–220; Taylor, I. N., (*C*) 383
Kermarec, N. *see* Liu, N., (*ESA*) A.128; 515–518
Kermarrec, N. *see* Mahé, V., (*ESA*) A.109
Kerr, K. A. *see* Buckmaster, H. A., (*C*) 598–599
Kettler, D. *see* Crozier, T. A. 47–53
Key, A. *see* Langton, J. A. 126–130
Kick, O. *see* Geiger, C., (*ESA*) A.14
Kidd, J. F. *see* Cobley, M. 576–578
Kinsella, J. Ketorolac postoperative analgesia, (*C*) 113
Kirollos, R. *see* Murphy, P. G. 583–586
Kirton, C. *see* Innes, P., (*ESA*) A.167
Kirvelä, M., Yli-Hankala, A. and Lindgren, L. Total intravenous anaesthesia (TIVA) with propofol and alfentanil for renal transplantation, (*ESA*) A.81
Kirvelä, M. *see* Lindgren, L. 306–310
Kitching, A. J. and Rice, A. S. C. Extradural abscess in the postpartum period, (*C*) 703
Klement, W. *see* Wiesemes, R. 552–555
Klotz, K.-F. *see* Eleftheriadis, S., (*ESA*) A.3; Kuppe, H., (*ESA*) A.31
Knapik, P., Richardson, J. B. and McLellan, I. Core–peripheral temperature difference in early *vs* later extubation after coronary artery surgery, (*ESA*) A.69; Early postperfusion assessment of gas exchange and postoperative extubation outcome following coronary artery surgery, (*ESA*) A.61
Knight, T. L. *see* Kenna, J. G., (*ARS*) 484–485P
Knoll, R. *see* Geisslinger, G. 666–671
Knothe, C. *see* Boldt, J. 661–665
Knowles, P. F. *see* Halsall, P. J., (*C*) 599
Koblin, D. D., Laster, M. J. and Liu, J. Anaesthetic properties of dimethylthiourea 456–458
Kohn, W. *see* Perel, A., (*ESA*) A.117
Koscielniak-Nielsen, Z. J., Schierbeck, J., Stens Pedersen, H. L. and Perko, G. Flumazenil facilitates intraoperative arousal in scoliosis surgery, (*ESA*) A.157
Koshikawa, N. *see* Takada, K. 181–185
Koutsoukou-Dritsopoulou, A. *see* Wang, C. 63–69
Kowolik, M. J. *see* Ogilvy, A. J., (*ARS*) 476P
Kox, W. J. *see* Scherer, R. U. 689–690
Kozak Ribbens, G., Rodet, L., Borsarelli, J., Aubert, M. and Cozzone, P. J. Exercise and malignant hyperthermia: family investigations, (*ESA*) A.92
Kraemer, S. *see* Spies, C., (*ESA*) A.110
Krämer, J. *see* Striebel, H. W., (*ESA*) A.208
Kremastinou, F. *see* Georgiou, L., (*ESA*) A.60
Krivosic-Horber, R. *see* Bromberg, N., (*ESA*) A.28
Krzeminska, E. K. *see* Field, L. M. 154–159
Kudynska, J. *see* Buckmaster, H. A., (*C*) 598–599
Kuhn, W. *see* Crozier, T. A. 47–53
Kuitunen, A., Hynynen, M., Salmenperä, M., Rasi, V., Järvinen, A., Scheinin, M., Neuvonen, P. J. and Fyhrquist, F. Anaesthesia affects plasma concentrations of vasopressin, von Willebrand factor and coagulation factor VIII in cardiac surgical patients 173–180
Kulka, P. J., Tryba, M., Menzel, C., Leurs, F. and Frankenberg, C. Preoperative clonidine improves postoperative renal function in CABG patients, (*ESA*) A.143
Kulkarni, P. and Carli, F. Effectiveness of core warming on net transfer of body heat across the skin, (*ESA*) A.70
Kulkarni, P., Matson, A., Bright, J., Pearson, J. and Carli, F. Clinical evaluation of the oesophageal heat exchanger in the prevention of perioperative hypothermia 216–218
Kumar, B., (editor) *MCQs in Anaesthesia: Basic Sciences*, (*R*) 117
Kuppe, H., Klotz, K.-F., Eleftheriadis, S., Gehring, H. and Gerling, W. Accuracy of processed auditory evoked response in predicting movement during cardiac surgery, (*ESA*) A.31
Kuppe, H. *see* Eleftheriadis, S., (*ESA*) A.3

Lacarelle, B. *see* Viviand, X., (*ESA*) A.150
Lachatre, G. *see* Nathan, N., (*ESA*) A.151
Lacoste, L., Karayan, J., Lehuedé, M. S., Ingrand, P. and Fusciardi, J. Direct, indirect or flexible laryngoscopy after thyroidectomy? (*ESA*) A.66
Lacoste, L., Karayan, J., Thomas, D., Vallet, T. and Fusciardi, J. Day 0 or day 3 laryngoscopy after thyroidectomy? (*ESA*) A.67
de La Coussaye, J. E., Eledjam, J. J., Bruelle, P., Peray, P. and Sassine, A. Lemakalim reverses ventricular conduction impairment induced by a large dose of bupivacaine in anesthetized dogs, (*ESA*) A.121
de La Coussaye, J. E. *see* Lefrant, J. Y., (*ESA*) A.18
Lafont, N. *see* Boogaerts, J., (*ESA*) A.200; Legros, F. J., (*ESA*) A.122
Lai, Y.-Y. *see* Tsai, Y.-C. 394–396
Laidlaw, J. M. *see* Arnold, C. 118
Laishley, R. S. Intermittent *vs* continuous extradural infusion of bupivacaine during labour, (*C*) 490
Lam, F. Y. Patient-controlled analgesia by proxy, (*C*) 113
Lamas, G. *see* Bodin, L., (*ESA*) A.179
Lamb, J. M., Murty, G. E., Slater, R. M. and Aitkenhead, A. R. Postoperative laryngeal function assessed by tussometry, (*ARS*) 478–479P
Lambert, D. G. and Hirst, R. A. Effects of morphine and its metabolites on opiate receptor binding and cyclic

adenosine-3′,5′-monophosphate (cAMP) formation in human neuroblastoma cells, (*ARS*) 475–476P

Lambert, D. G. *see* Atcheson, R., (*ARS*) 485P; Hirst, R. A., (*ARS*) 486P

Lamond, C. T., Robinson, D. L., Boyd, J. T. and Cashman, J. N. Addition of droperidol to PCA morphine: what is the optimal dose? (*ESA*) A.204

Lampl, E. and Dandoy, M. Priming of atracurium with magnesium, (*ESA*) A.139

Lamy, M. *see* Joris, J., (*ESA*) A.33

Landon, A. J., Matson, A. M., Royston, B. D., Hewlett, A. M., White, D. C. and Nunn, J. F. Components of the inspiratory–arterial isoflurane partial pressure difference 605–611

de Lange, J. J. *see* de Jong, J. R., (*ESA*) A.15; Wagemans, M. F. M., (*ESA*) A.213

Langham, B. T. and Harrison, D. A. The pressor response to venous cannulation: attenuation by prior infiltration with local anaesthetic 519–521

Langton, J. A., Murphy, P. J., Barker, P., Key, A. and Smith, G. Measurement of the sensitivity of upper airway reflexes 126–130

Langton, J. A. *see* Erskine, R. J., (*ARS*) 478P; 574–575; Murphy, P. J. 131–134

Larsen, R. *see* Molter, G. 428–433

de Lassale, M. E. *see* Rouby, J. J., (*ESA*) A.181

Laster, M. J. *see* Koblin, D. D. 456–458

Latson, T. W. and O'Flaherty, D. Effects of surgical stimulation on autonomic reflex function: assessment by changes in heart rate variability 301–305

Latto, P. *see* Rosen, M., (*R*) 601

Laurent, P. *see* Bodin, L., (*ESA*) A.179

Laussen, P. C. *see* Wolf, A. R. 654–660

Law Min, J.-C., Hood, J. R., Campkin, N. and Feldman, S. A. Recovery of atracurium and vecuronium neuromuscular block in the isolated forearm, (*ARS*) 480–481P

Laxenaire, M. C. *see* Bermejo, N. 322–325

Layfield, D. J. *see* Morris, R. W., (*ESA*) A.2

Le Bars, D. *see* Guirimand, F., (*ESA*) A.116

Lebrault, C. *see* Alfonsi, P., (*ESA*) A.74; Chauvin, M., (*ESA*) A.115

Le Bret, F. *see* Goarin, J. P., (*ESA*) A.193; Gosgnach, M., (*ESA*) A.21

Lee, J. H. *see* Jawan, B. 639–641

Lee, M. G. Bacterial retention properties of heat and moisture exchange filters, (*C*) 382

Lee, R. C., Cravalho, E. G. and Burke, J. F., (editors) *Electrical Trauma: the Pathophysiology, Manifestations and Clinical Management*, (*R*) 601

Lefrant, J. Y., de La Coussaye, J. E., Aya, G., Saïssi, G. and Eledjam, J. J. Cardiac output (CO) measurement: comparison of esophageal Doppler (ED) *vs* thermodilution (TD), (*ESA*) A.18

Legros, F. J., Lafont, N., Donnay, M. and Boogaerts, J. Motor blockade and absence of local nerve toxicity induced by liposomal bupivacaine injected into the axillary brachial plexus of rabbits, (*ESA*) A.122

Legros, F. J. *see* Boogaerts, J., (*ESA*) A.200

Lehmann, K. A. *see* Radbruch, L., (*ESA*) A.212

Lehuedé, M. S. *see* Lacoste, L., (*ESA*) A.66

Leicht, C. H. *see* Vasdev, G. M. S., (*C*) 703–704

Leijala, M. *see* Puhakka, K. 149–153

Lejus, C. *see* Malinovsky, J.-M. 617–620

Lemaire, F. *see* Artigas, A., (*R*) 117

Lenoir, B. *see* Descraques, C., (*ESA*) A.127

Le Normand, Y. *see* Malinovsky, J.-M. 617–620

Lenzlinger, P. M. *see* Alon, E., (*ESA*) A.12

Lepage, J. Y., Garrec, F., Malinovsky, J. M., Cozian, A. and Pinaud, M. Effects of plasma volume substitution on right ventricle volumes and function using Elohes® and Plasmion®, (*ESA*) A.35

Lepage, J.-Y. *see* Malinovsky, J.-M. 617–620

Le Pelley, E., Chataigneau, T., Richer, J.-P., Tricoche, R. and Fusciardi, J. Does captopril modify the arterial response to vasopressor substances? (*ESA*) A.48

Lequeau, F., Bourgain, J. L., Castaigne, D. and Samama, M. Use of aprotinine during cytoreductive surgery of ovarian cancer, (*ESA*) A.97

Leung, R. K. W. *see* Gin, T. 311–316

Leurs, F. *see* Kulka, P. J., (*ESA*) A.143

Levarlet, M. *see* Bardoczky, G. I. 499–502

Levy, D. M. and Tunstall, M. E. Preoperative drinking and gastric contents, (*C*) 701–702

Lewis, S. A. *see* Phillips, A. S., (*ARS*) 484P

Lherm, T. *see* Rouby, J. J., (*ESA*) A.181

Lienhart, A., Deriaz, H., Desnault, H., Masini, J. P. and Delva, E. Is Burkitt's lymphoma an etiology or a differential diagnosis of malignant hyperthermia? (*ESA*) A.93

Lienhart, A. *see* Camus, Y., (*ESA*) A.72; Debaene, B., (*ESA*) A.142; Vassilieff, N., (*ESA*) A.71

Lindgren, L., Yli-Hankala, A., Randell, T., Kirvelä, M., Scheinin, M. and Neuvonen, P. J. Haemodynamic and catecholamine responses to induction of anaesthesia and tracheal intubation: comparison between propofol and thiopentone 306–310

Lindgren, L. *see* Kirvelä, M., (*ESA*) A.81; Watanabe, H. 94–95; Yli-Hankala, A. 54–57

Lipfert, P. *see* Wiesemes, R. 552–555

Lippmann, M. and Ginsburg, R. Neuromuscular blockers in day-case surgery: is speed of onset more important than duration of action? (*C*) 235

Lipszyc, M. *see* Engelman, E., (*ESA*) A.144

Lipton, J. M. *see* Sharkey, A. 449–450

Lisander, B. Evaluation of the analgesic effect of metoclopramide after opioid-free analgesia 631–633

Liu, J. *see* Koblin, D. D. 456–458

Liu, N., Bonnet, F., Delaunay, L., Kermarec, N. and D'Honneur, G. Partial reversal of the effects of extradural clonidine by oral yohimbine in postoperative patients 515–518

Liu, N., Catoire, P., Rosso, J., Saada, M. and Bonnet, F. Evaluation in intensive care of the fraction area change obtained by automatic border detection, (*ESA*) A.25

Liu, N., Montefiore, A., Kermarec, N., Beydon, L. and Bonnet, F. Postdural puncture headaches are not related to the duration of spinal catheter placement, (*ESA*) A.128

Ljungqvist, O. *see* Odeberg, S., (*ESA*) A.34

Lockie, J. *see* Innes, P., (*ESA*) A.167

Lockley, S. M. *see* Collier, C. B. 462–465

Lofaso, F. *see* Beydon, L., (*ESA*) A.4

Loh, L. *see* Reeder, M. K. 119; 119; 119

Loufoua, J. *see* Freysz, M., (*ESA*) A.46

Lovell, G. G. *see* Head-Rapson, A. G., (*ARS*) 487P

Luciani, J. *see* Mouquet, C., (*ESA*) A.82; (*ESA*) A.83

Lucke, F. *see* Savoia, G., (*ESA*) A.159

Luhmann, I. *see* Striebel, H. W., (*ESA*) A.208

Lundberg, J. *see* Raner, C., (*ESA*) A.49

Lunghi, P. *see* Foppoli, R., (*ESA*) A.132

Lunn, J. N., Devlin, H. B., Hoile, R. W. and Campling, E. A. Editorial II—the National Confidential Enquiry into Perioperative Deaths, (*C*) 382

Lynch, M. *see* Alcock, R. 34–37

Lyons, G. Best Quincke point needle for Caesarean section, (*ESA*) A.174

McAleer, S. *see* Arnold, C. 118

McCarroll, S. M. *see* Joshi, G. P. 87–88

McCarthy, G. and Mirakhur, R. K. *MCQ for the Higher Examination in Clinical Pharmacology*, (*R*) 241

McCarthy, R. *see* Polster, M. R. 612–616

McCartney, C. A. *see* Nathanson, M. H., (*ARS*) 481–482P

McClure, J. H. and Wildsmith, J. A. W., (editors) *Conduction Blockade for Postoperative Analgesia: Mechanisms and Management*, (*R*) 239

McClure, J. H. *see* Wildsmith, J. A. W., (*C*) 112

McCollum, C. N. *see* McKavney, M., (*ARS*) 475P

McCoy, D., O'Connor, M., Cunningham, A. and Dwyer, R. Influence of positive pressure ventilation on myocardial ischaemia after abdominal aortic aneurysm repair, (*ESA*) A.43

McCoy, D. *see* Doyle, M., (*ARS*) 486–487P

McCoy, E. *see* Maddineni, V. R. 694–695

McCrae, A. F. and Wildsmith, J. A. W. Prevention and treatment of hypotension during central neural block 672–680

McDaid, C. M. *see* Phillips, A. S., (*ARS*) 484P

Macdonald, A. G. John Henry Hill Lewellin: The first etherist in Glasgow 228–234

McDonald, P. F. *see* Coghlan, S. F. E. 89–91

McEwan, T. *see* Alcock, R. 34–37

McFadzean, W. *see* Doyle, E. 542–555

McGinn, A. *see* Baker, A. B. 259–266

McHale, S. and Carli, F. Continuous subarachnoid infusion of 0.125% bupivacaine for analgesia during labour, (*C*) 701

MacIntyre, D. *see* Crawford, M. 419–422

McKavney, M., Corson, R. J., Hanbury, A., Mortimer, A. J., Keegan, M., McCollum, C. N. and Campbell, I. T. Effect of selective cell separation on respiratory function after aortic aneurysm surgery, (*ARS*) 475P

McKenzie, P. J. *see* Reeder, M. K. 119

Mackenzie, S. J. *see* Runcie, C. J. 192–195

McLaughlan, G. A. *see* Berthoud, M. C. 423–427

McLellan, I. *see* Knapik, P., (*ESA*) A.61; (*ESA*) A.69

McLeod, G. A., Carson, D. and Bannister, J. "Concorde nose" in Whitacre spinal needles, (*C*) 593
McMahon, A. J., Baxter, J. N. and O'Dwyer, P. J. Metabolic effects of cholecystectomy, (*C*) 493–494
McMahon, S. B. *see* Rice, A. S. C., (*C*) 594
McMenemin, I. Subdural catheterization and cord damage, (*C*) 384
McMenemin, I. *see* Dryden, C. M. 508–510
McMurray, T. J. *see* Phillips, A. S., (*ARS*) 484P
McQuillan, P. *see* Young, J. D. 58–62
McSwiney, M. Blood loss during total hip replacement, (*C*) 236
Maddineni, V. R., Mirakhur, R. K., Cooper, R. and McCoy, E. Potency estimation of mivacurium: comparison of two different modes of nerve stimulation 694–695
Maddineni, V. R. *see* Cooper, R., (*ARS*) 482P
Madsen, J. B. *see* Crawford, M. E. 642–646
Maghrebi, H. *see* Bodin, L., (*ESA*) A.191
Mahajan, R. P., Hennessy, N. and Aitkenhead, A. R. Lung function after vecuronium pretreatment in elderly patients, (*ARS*) 482–483P
Mahajan, R. P., Murty, G. E., Singh, P. and Aitkenhead, A. R. Laryngeal function as assessed by tussometry following topical anaesthesia, (*ESA*) A.68
Mahajan, R. P. *see* Hennessy, N., (*ARS*) 475P
Mahé, V., Kermarrec, N. and Ecoffey, C. External ventricular CSF drains infections, (*ESA*) A.109
Mahé, V. *see* Moulay, N., (*ESA*) A.108
Malinovsky, J.-M., Lejus, C., Servin, F., Lepage, J.-Y., Le Normand, Y., Testa, S., Cozian, A. and Pinaud, M. Plasma concentrations of midazolam after i.v., nasal or rectal administration in children 617–620
Malinovsky, J. M. *see* Lepage, J. Y., (*ESA*) A.35
Malinowsky, J.-M. *see* Benhamou, D., (*ESA*) A.120
Mallett, S. V. and Cox, D. J. A. Haemostasis and thrombelastography: a cautious note, (*C*) 699–700
Mannion, D. *see* Doyle, M., (*ARS*) 486–487P
Mansoor, K. *see* Jedeiken, R., (*C*) 491–492
Mapleson, W. W. *see* Davis, N. R. 248–258; 711
Marana, E. *see* Crea, M. A., (*ESA*) A.63
Marcassa, A., Sorbara, C., Stellin, G., Pittarello, D. and Giron, G. P. Extracorporeal membrane oxygenation for postoperative cardiac support in newborn infants: first clinical data, (*ESA*) A.168
Marjot, R. Pressure exerted by the laryngeal mask airway cuff upon the pharyngeal mucosa 25–29; Pressure exerted by the laryngeal mask airway cuff upon the pharyngeal mucosa 711
Marsh, D. *see* O'Kelly, S. W., (*C*) 239
Martin, C., Auffray, J.-P., Potié, F. and Gouin, F. Comparison of two therapeutic strategies of septic shock, (*ESA*) A.190
Martin, C., Papazian, L., Perrin, G., Saux, P. and Gouin, F. Preservation of humidity and heat of respiratory gases in patients with minute ventilation > 10 l/min, (*ESA*) A.20
Martin, C., Saux, P., Mege, J.-L., Perrin, G. and Gouin, F. Septic shock: effect of a goal-directed therapy on oxygen metabolism and serum cytokine levels, (*ESA*) A.189
Martin, C. *see* Albanese, J., (*ESA*) A.107; Viviand, X., (*ESA*) A.150
Martin, D. C., Pruett, J. K. and Aronstam, R. S. Test-tube equilibration of volatile anaesthetic concentrations 365–367
Martin, D. F. *see* Watt, T., (*ARS*) 477P
Martin, E. *see* Geiger, C., (*ESA*) A.14; Motsch, J., (*ESA*) A.155; Rauch, H., (*ESA*) A.30
Martin, P. G. *see* Gupta, N. K., (*C*) 699
Martínez, J. L. *see* Martínez Urionabarrenetxea, K., (*ESA*) A.187; Pérez Arancón, J. L., (*ESA*) A.188
Martínez Urionabarrenetxea, K., Pérez Arancón, J. L., Yoldi, J. I., Camarero, A. and Martínez, J. L. Molecular mediators and post-bacteraemic phase, (*ESA*) A.187
Martínez Urionabarrenetxea, K. *see* Pérez Arancón, J. L., (*ESA*) A.188
Martner, J. *see* Raner, C., (*ESA*) A.49; Sundeman, H., (*ESA*) A.50
Mashimo, T. *see* Tomi, K. 684–686
Masini, J. P. *see* Lienhart, A., (*ESA*) A.93
Masterson, G. R. *see* Beck, G. N., (*ARS*) 483P
Mata, E. *see* Bermejo, N. 322–325
Mather, C. Preoperative drinking and gastric contents, (*C*) 702
Matson, A. *see* Kulkarni, P. 216–218
Matson, A. M. *see* Landon, A. J. 605–611
May, A. E. *see* Vickers, R. J. 214–215
Mayer, M. *see* Doenicke, A., (*C*) 491
Maze, M. *see* Salonen, M., (*ESA*) A.113
Mazoit, J. X. *see* Butscher, K., (*ESA*) A.201
Mazoyer, E. *see* Samama, C. M., (*ESA*) A.100
Meakin, G. *see* Barrie, J. R. 468–470; Beatty, P. C. W., (*C*) 707
Mearns, A. J. *see* Berrisford, R. G. 201–204
Medley, C. *see* Murphy, D. F. 298–300
Mege, J.-L. *see* Martin, C., (*ESA*) A.189
Mehta, V. *see* Hohner, P., (*ESA*) A.23; (*ESA*) A.26
Meier-Hellmann, A., Hannemann, L., Weyandt, D., Heiss-Dunlop, W. and Reinhart, K. The effect of dobutamine and norepinephrine on global and splanchnic O_2 consumption, (*ESA*) A.185
Meistelman, C., Fiset, P., O'Kelly, B., Frossard, J., Plaud, B. and Ecoffey, C. The pharmacokinetics of rocuronium in pediatric patients: a pooled data analysis, (*ESA*) A.138
Meistelman, C. *see* Debaene, B., (*ESA*) A.142; Plaud, B., (*ESA*) A.141
Menigaux, C., Hamza, J., Bougnières, P. and Saint-Maurice, C. Neonatal glycemia: does the maternal i.v. fluid regimen during labor make a difference? (*ESA*) A.175
Menon, G. and Allt-Graham, J. Anaesthetic implications of the anti-cardiolipin antibody syndrome 587–590
Menzel, C. *see* Kulka, P. J., (*ESA*) A.143
Méray, J. *see* Vereczkey, Z., (*ESA*) A.64
Meretoja, O. A., Brandom, B. W., Taivainen, T. and Jalkanen, L. Supra-additivity between atracurium and vecuronium, (*ESA*) A.140
Mergaert, C., Rolly, G. and Versichelen, L. Target-controlled intravenous sedation with propofol, (*ESA*) A.149
Mersch, Y. *see* Hennart, D., (*ESA*) A.202
Messeter, K. *see* Åkeson, J., (*ESA*) A.111
Mestre, D. *see* Paut, O., (*ESA*) A.10
Michael, R. F. *see* Morris, R. W., (*ESA*) A.2
Michel, M. Z., Goodman, N. W. and Aitkenhead, A. R. *Essay Plans for Anaesthesia Exams*, (*R*) 709
Mimoz, O., Edouard, A., Beydon, L., Bonnet, F. and Samii, K. Reassessment of bronchoalveolar lavage in the diagnosis of post traumatic pulmonary fat embolism, (*ESA*) A.180
Mion, G. *see* Delayance, S., (*ESA*) A.45; Descraques, C., (*ESA*) A.127
Mirakhur, R. K., Cooper, R. A., Clarke, R. S. J. and Boules, Z. Neuromuscular blockers in day-case surgery: is speed of onset more important than duration of action? (*C*) 235
Mirakhur, R. K. *see* Cooper, R., (*ARS*) 482P; McCarthy, G., (*R*) 241; Maddineni, V. R. 694–695
Mirow, N. *see* Weiss, M. 317–321
Møiniche, S. *see* Dahl, J. B., (*C*) 379
Molke Jensen, F. *see* Crawford, M. E. 642–646
Molter, G., Larsen, R., Peters, U., Bauch, U. and Sefrin, R. Haemodynamic changes produced by inhalation anaesthetics in the presence of phosphodiesterase inhibition 428–433
Monedero, P., Carrera, J., Catalá, J., Carrascosa, F. and Arroyo, J. L. Blood requirements reduction in orthotopic liver transplantation with aprotinin, (*ESA*) A.98
Monedero, P. *see* Carrera, J., (*ESA*) A.77; Hidalgo, F., (*ESA*) A.99; de los Ríos, J., (*ESA*) A.75
Monells, J. *see* Fernandez, S., (*ESA*) A.119
Moneret-Vautrin, D. A. *see* Bermejo, N. 322–325
Monin, S. *see* Jamali, S., (*ESA*) A.160; Nègre, I., (*ESA*) A.203
Monrigal, C. *see* Granry, J. C., (*ESA*) A.32
Monrigal, J. P. *see* Granry, J. C., (*ESA*) A.32
Montasser, A. M. Propofol for tracheal intubation in paediatric outpatient anaesthesia, (*ESA*) A.161
Montefiore, A. *see* Liu, N., (*ESA*) A.128
Moore, N. *see* Moritz, F. 451–453
Mora, C. *see* Foppoli, R., (*ESA*) A.132
Morgan, B. *see* Robson, S. C. 634–638
Morgan, R. J. and Pollard, B. J. Prediction of infusion rate of vecuronium to maintain steady state using the bolus test dose technique, (*ARS*) 481P
Moritz, F., Petit, J., Kaeffer, N., Oksenhendler, G., Papion, H., Hecketsweiler, B., Moore, N. and Winckler, C. Metabolic effects of propofol and flunitrazepam given for sedation after aortic surgery 451–453
Morris, R. W., Ernst, E., Greaves, D. J., Layfield, D. J. and Michael, R. F. An audit of the incidence and costs associated with post operative nausea and vomiting (PONV) following major gynaecological surgery in an inpatient population, (*ESA*) A.2
Mortimer, A. J. *see* McKavney, M., (*ARS*) 475P
Morton, N. S. *see* Doyle, E. 542–555; Runcie, C. J. 192–195
Motsch, J., Baller, S., Bach, A., Aderjan, R. and

Martin, E. Midazolam premedication: a forensic approach to pharmacokinetics and amnesia, (*ESA*) A.155

Motsch, J. *see* Geiger, C., (*ESA*) A.14

Moulay, N., Mahé, V., Descorps-Déclère, A., Cosson, C. and Ecoffey, C. Cardiac function in aneurysmal subarachnoid haemorrhage, (*ESA*) A.108

Mouquet, C., Carayon, A., Clergue, F., Luciani, J., Bitker, M. and Viars, P. Volume loading and hormonal factors in the prevention of acute tubular necrosis in kidney transplantation, (*ESA*) A.83

Mouquet, C., Carayon, A., Ourahma, S., Bitker, M.-O. and Viars, P. Is the vasoconstrictive effect of cyclosporine mediated by endothelin in kidney transplantation? (*ESA*) A.84

Mouquet, C., Luciani, J., Bitker, M.-O. and Viars, P. Prevention of acute tubular necrosis by volume loading in kidney transplantation, (*ESA*) A.82

Mouren, S. *see* Delayance, S., (*ESA*) A.45; Fellahi, J. L., (*ESA*) A.44

Mourgeon, E. *see* Vivien, B., (*ESA*) A.183

Moyle, J. T. B. *see* Davey, A., (*R*) 240

Mueller, R. F. *see* Ball, S. P. 70–75

Muir, A. D. *see* Reeder, M. K. 119; 119; 119

Mulazzi, D., Calappi, E. and Croci, M. The respiratory compliance in normal and obese subjects during anaesthesia, (*ESA*) A.54

Müller, C. *see* Heil, T., (*ESA*) A.88

Muller, G. *see* Van Obbergh, L. J., (*ESA*) A.164

Munday, I. T. and Jones, R. M. Anq 9040: effect of twice the ED$_{95}$ dose, (*ARS*) 480P

Munday, I. T. *see* Watson, N. A., (*ARS*) 479P

Munglani, R., Andrade, J., Sapsford, D. J., Baddeley, A. and Jones, J. G. Validation of coherent frequency of the EEG as a measure of consciousness during anaesthesia, (*ARS*) 483–484P

Murai, T. *see* Takada, K. 181–185

Murat, I., Bernière, J. and Constant, I. Evaluation of the efficacy of forced-air warmer (Bair Hugger) during spinal surgery in children, (*ESA*) A.165

Murat, I., Delorme, M., Piat, V. and Dubois, M. C. Evaluation of a forced-air warmer (Bair-Hugger) in maintaining body temperature in infants during cleft palate surgery, (*ESA*) A.166

Murga, G. *see* Samsó, E., (*ESA*) A.205

Murphy, D. F. and Medley, C. Preoperative indomethacin for pain relief after thoracotomy: comparison with postoperative indomethacin 298–300

Murphy, P. G., Jackson, R., Kirollos, R., Gibson, J. S. and Chennels, P. Adult respiratory distress syndrome after attempted strangulation 583–586

Murphy, P. G. *see* Ogilvy, A. J., (*ARS*) 476P

Murphy, P. J., Langton, J. A., Barker, P. and Smith, G. Effect of oral diazepam on the sensitivity of upper airway reflexes 131–134

Murphy, P. J. *see* Erskine, R. J., (*ARS*) 478P; 574–575; Langton, J. A. 126–130

Murphy, W. G., Davies, M. J. and Eduardo, A. The haemostatic response to surgery and trauma 205–213

Murty, G. E. *see* Lamb, J. M., (*ARS*) 478–479P; Mahajan, R. P., (*ESA*) A.68

Mya, G. H. *see* Jones, R. D. M. 286–292

Myles, A. P., Calow, P. and Reilly, C. S. Clonal variation in response to enflurane anaesthesia with *Daphnia magna*, (*ARS*) 476–477P

Mythen, M., Browne, D., Hamilton-Davies, C. and Webb, A. Gastric mucosal perfusion is better preserved during cardiac surgery when isoflurane rather than enflurane or propofol is used to maintain anaesthesia, (*ESA*) A.29

Nakajima, R., Nakajima, Y. and Ikeda, K. Minimum alveolar concentration of sevoflurane in elderly patients 273–275

Nakajima, Y. *see* Nakajima, R. 273–275

Narchi, P. *see* Aubrun, F., (*ESA*) A.198; Hamza, J., (*ESA*) A.171

Narcisse, F. *see* Nathan, N., (*ESA*) A.151

Nath, S. and Ehrenström Reiz, G. Treatment of cancer pain with morphine (MO)—A double blind study of extradural (ED) *versus* intramuscular (im) routes of administration, (*ESA*) A.211

Nathan, N., Debord, J., Narcisse, F., Dupuis, J. L., Lachatre, G. and Feiss, P. Pharmacokinetics of propofol and its conjugates after continuous infusion in normal and renal failure patients, (*ESA*) A.151

Nathanson, M. H., McCartney, C. A., Ferguson, C. and Jordan, M. J. Onset of action of a small dose of vecuronium, (*ARS*) 481–482P

Nebauer, A. E. *see* Doenicke, A., (*C*) 491

Nègre, I., Guéneron, J. P., Jamali, S., Monin, S. and Ecoffey, C. Preemptive analgesia with epidural morphine, (*ESA*) A.203

Nelson, T. E. Combined caffeine–halothane test for malignant hyperthermia, (*C*) 597–598

Nelson, V. *see* Bennett, S., (*ESA*) A.152

Neumann, T. *see* Heil, T., (*ESA*) A.88; Spies, C., (*ESA*) A.110

Neuvonen, P. J. *see* Kuitunen, A. 173–180; Lindgren, L. 306–310

Newton, D. E. F. *see* Thornton, C., (*C*) 705

Ng, S. *see* Rosen, M., (*R*) 601

Ngan Kee, W. D. Extradural abscess in the postpartum period, (*C*) 704

Nishikawa, T. Acute haemodynamic effect of sodium bicarbonate in canine respiratory or metabolic acidosis 196–200

Nishimura, M. *see* Tomi, K. 684–686

Nishimura, S. *see* Tomi, K. 684–686

Nolan, A. and Reid, J. Pharmacokinetics of propofol administered by infusion in dogs undergoing surgery 546–551

Nolan, K. M., Winyard, J. A. and Goldhill, D. R. Comparison of nasal cannulae with face mask for oxygen administration to postoperative patients 440–442

Nordström, O. and Sandin, R. Delayed presentation of an extradural abscess in a patient with alcohol abuse 368–369

Norman, R. I. *see* Appadu, B., (*ARS*) 477P

Novotny, G. E. K. *see* Wiesemes, R. 552–555

Nunn, J. F. *see* Landon, A. J. 605–611

Nyarwaya, J.-B. *see* Dupont, H., (*ESA*) A.9

Nyström, E., Jansson, E., Wenngren, B.-I., Sharma, R., Clergue, F. and Reiz, S. Diaphragmatic function after bupivacaine cervical extradural analgesia for chronic pain therapy, (*ESA*) A.65

Nyström, E. *see* Reiz, S., (*ESA*) A.52

O'Connor, B. *see* Salonen, M., (*ESA*) A.113

O'Connor, L. *see* Green, D. W. 626–630

O'Connor, M. *see* McCoy, D., (*ESA*) A.43

Odeberg, S., Ljungqvist, O., Gannedahl, P., Svenberg, T. and Sollevi, A. Influence of pneumoperitoneum and posture on hemodynamic and stress responses during anaesthesia for laparoscopic surgery, (*ESA*) A.34

O'Dwyer, P. J. *see* McMahon, A. J., (*C*) 493–494

O'Flaherty, D. *see* Latson, T. W. 301–305

Ogilvy, A. J., Whiteley, S. M., Kowolik, M. J. and Murphy, P. G. Effect of propofol on neutrophil respiratory burst, (*ARS*) 476P

Oh, T. E., Bhatt, S. B. and Tomlinson, B. Metabolic effects of dobutamine, (*C*) 237–238

Oh, T. E. *see* Aun, C. S. T. 647–653; Tan, I. K. S. 267–272

Ojanen, R., Kaukinen, S., Seppälä, E., Kaukinen, L. and Vapaatalo, H. Inhibition of increase of blood thromboxane concentration by acetylsalicylic acid after release of tourniquet in lower extremity operations, (*ESA*) A.94

O'Kelly, B. *see* Meistelman, C., (*ESA*) A.138

O'Kelly, S. W. and Marsh, D. Face masks and spinal anaesthesia, (*C*) 239

Oksenhendler, G. *see* Moritz, F. 451–453

Olsfanger, D. *see* Jedeiken, R., (*C*) 491–492

O'Meara, M. E. *see* Aun, C. S. T. 647–653; Gin, T. 311–316

Ooi, L. G., O'Shea, P. J. and Wood, A. J. Use of esmolol in the postbypass management of hypertrophic obstructive cardiomyopathy 104–106

Ooi, R., Fawcett, W. J., Soni, N. and Riley, B. Extra inspiratory work of breathing imposed by cricothyrotomy devices 17–21; Extra inspiratory work of breathing imposed by cricothyrotomy devices 494

Ooi, R. *see* Joshi, P., (*C*) 238

O'Regan, M. *see* Doyle, M., (*ARS*) 486–487P

Oris, B. *see* Puybasset, L., (*ESA*) A.39

Orliaguet, G., Plaud, B., Calmatte, S. and Ecoffey, C. Neuromuscular blockade following mivacurium in children during N$_2$O–halothane, (*ESA*) A.163

O'Shea, P. J. *see* Ooi, L. G. 104–106

Österlund, B., Johansson, G. and Reiz, S. Cardiac output determined from pulmonary gas exchange, (*ESA*) A.19

Östman, M., Karling, M., Karp, K., Teien, D. and Reiz, S. Dipyridamole-TEE and 24 h Holter-ECG as preoperative screening tests for coronary artery disease in patients with abdominal aortic aneurysm, (*ESA*) A.22

O'Sullivan, G. *see* Polster, M. R. 612–616

Ouardali, F. *see* Fellahi, J. L., (*ESA*) A.44

Ourahma, S. *see* Guesde, R., (*ESA*) A.79; Mouquet, C., (*ESA*) A.84

Özgök, A. *see* Durak, P., (*ESA*) A.95; (*ESA*) A.96

Pak, M. *see* Tomi, K. 684–686

Palayiwa, E., Grint, E., Winyard, J., Flynn, P. J. and Strunin, L. Evaluation of the Rascal II monitor, (*ARS*) 485P

Palazzo, M. and Evans, R. Logistic regression analysis of fixed patient factors for postoperative sickness: a model for risk assessment 135–140

Panadero, A. *see* Carrera, J., (*ESA*) A.77

Papazian, L. *see* Martin, C., (*ESA*) A.20

Papion, H. *see* Moritz, F. 451–453

Páramo, J. A. *see* Hidalgo, F., (*ESA*) A.99

Park, G. R. Hypertonic solutions in acute massive haemorrhage, (*C*) 706

Park, G. R. *see* Jacobson, W. 522–526; Polster, M. R. 612–616

Parker, C. J. R. and Hunter, J. M. Pharmacokinetic/pharmacodynamic modelling of atracurium, (*C*) 111–112; Relationship between volume of distribution of atracurium and body weight 443–445

Parker, C. J. R., Hunter, J. M. and Snowdon, S. L. Effect of age, gender and anaesthetic technique on the pharmacodynamics of atracurium 38–41

Parker, C. J. R. *see* Head-Rapson, A. G., (*ARS*) 487P

Pasch, T. and Hawelski, T. Propofol anaesthesia with spontaneous breathing for extracorporeal shock wave lithotripsy, (*ESA*) A.153

Pasch, T. *see* Alon, E., (*ESA*) A.12

Pats, B. *see* Descraques, C., (*ESA*) A.127

Paut, O., Vercher, J. L., Blin, O., Mestre, D. and Camboulives, J. Evaluation of saccadic eye movements as an objective test during recovery from anesthesia, (*ESA*) A.10

Paxton, S. *see* Inglis, T. J. J. 527–531

Payen, D. *see* Jacob, L., (*ESA*) A.85

Peachey, T. *see* Alcock, R. 34–37

Peacock, J. E. and Reilly, C. S. Different rates of injection of propofol, (*C*) 383–384

Peacock, J. E. *see* Berthoud, M. C. 423–427; Williams, O. A., (*ARS*) 479P

Pearson, J. *see* Kulkarni, P. 216–218

Peat, S. J. *see* Hanna, M. H. 511–514

Peltola, K. *see* Puhakka, K. 149–153

Pendeville, P. E. *see* Van Boven, M. J., (*ESA*) A.87

Pennant, J. H. *see* Van Elstraete, A. C. 691–693

Penzo, D. *see* Armellin, G., (*ESA*) A.104

Pepperman, M. *see* Skoyles, J., (*E*) 603–604

Peray, P. *see* de La Coussaye, J. E., (*ESA*) A.121

Perdrix, J. P. *see* Py, C., (*ESA*) A.57

Pere, P., Pitkänen, M., Tuominen, M., Edgren, J. and Rosenberg, P. H. Clinical and radiological comparison of perivascular and transarterial techniques of axillary brachial plexus block 276–279

Perel, A., Shneider, A. and Kohn, W. Isoproterenol reverses the MAC decreasing effect of esmolol in rats, (*ESA*) A.117

Perel, A. *see* Coriat, P., (*ESA*) A.38; Preisman, S., (*ESA*) A.51; (*ESA*) A.124

Pérez Arancón, J. L., Martínez Urionabarrenetxea, K., Yoldi, J. I., Camarero, A. and Martínez, J. L. Molecular mediators and cardiac surgery, (*ESA*) A.188

Pérez Arancón, J. L. *see* Martínez Urionabarrenetxea, K., (*ESA*) A.187

Perilli, V. *see* Crea, M. A., (*ESA*) A.63

Perko, G. *see* Koscielniak-Nielsen, Z. J., (*ESA*) A.157

Perrin, G. *see* Martin, C., (*ESA*) A.20; (*ESA*) A.189

Persaud, S. J. *see* Desborough, J. P., (*ESA*) A.91; 221–222

Peters, U. *see* Molter, G. 428–433

Petersen-Felix, S. and Zbinden, A. M. Brain partial pressures of isoflurane and nitrous oxide, (*C*) 704–705

Petit, J. *see* Moritz, F. 451–453

Pfeiffer, U. *see* Preisman, S., (*ESA*) A.51

Phillips, A. S., McDaid, C. M., McMurray, T. J. and Lewis, S. A. Does propofol supplemented anaesthesia affect neurophysiological outcome following cardiopulmonary bypass? (*ARS*) 484P

Phillips, S., Hutchinson, S. and Davidson, T. Preoperative drinking and gastric contents, (*C*) 702–703; Preoperative drinking does not affect gastric contents 6–9

Phillips, S., Hutchinson, S. E., Bayly, P. and Hollway, T. E. Adrenaline-induced hypotension in neurosurgery 687–688

Piat, V. *see* Murat, I., (*ESA*) A.166

Piccinni, P., Tripepi, A., Rossaro, L., De Zen, F. and Pierri, A. Oxygen consumption is dependent upon oxygen delivery in cirrhotics undergoing liver transplantation, (*ESA*) A.78

Pierri, A. *see* Piccinni, P., (*ESA*) A.78

Pietzsch, S. *see* Biro, P., (*ESA*) A.156

Pignaud, G. *see* Samama, C. M., (*ESA*) A.100

Pinaud, M. *see* Lepage, J. Y., (*ESA*) A.35; Malinovsky, J.-M. 617–620

Pironkov, A. *see* Gosgnach, M., (*ESA*) A.6

Pitkänen, M. *see* Pere, P. 276–279; Rosenberg, P. H., (*ESA*) A.129

Pittarello, D. *see* Armellin, G., (*ESA*) A.104; Marcassa, A., (*ESA*) A.168

Plastow, S. E. and Weisz, M. T. Transthoracic endoscopic sympathectomy, (*C*) 492

Platt, N. D. Xylometazoline and porphyria, (*C*) 491

Plaud, B., Proost, J. H., Wierda, J. M. K. H., Debaene, B., Barré, J. and Meistelman, C. Concentration–effect relationship at the vocal cords and the adductor pollicis following rocuronium administration, (*ESA*) A.141

Plaud, B. *see* Meistelman, C., (*ESA*) A.138; Orliaguet, G., (*ESA*) A.163

Plourde, G. Effect of nitrous oxide on auditory evoked potentials, (*C*) 379–380

Poelaert, J. *see* De Deyne, C., (*ESA*) A.16; (*ESA*) A.106

Poete, P. *see* Rouby, J. J., (*ESA*) A.181

Pol, A. *see* Bromberg, N., (*ESA*) A.28

Pollard, B. J. *see* Morgan, R. J., (*ARS*) 481P; Rittoo, D. B., (*ARS*) 486P

Pollock, J. *see* Crawford, M. 419–422

Pollock, J. S. S. and Kenny, G. N. C. Effects of lorazepam on oxygen saturation before cardiac surgery 219–220

Polster, M. R., Gray, P. A., O'Sullivan, G., McCarthy, R. and Park, G. R. Comparison of the sedative and amnesic effects of midazolam and propofol 612–616

Pommerening, J. *see* Striebel, W. H., (*ESA*) A.209

Porkkala, T. *see* Yli-Hankala, A. 54–57

Portilla, M. *see* Beaussier, M., (*ESA*) A.37

Potié, F. *see* Martin, C., (*ESA*) A.190

Potter, F. A. Explaining risk to patients, (*C*) 381

Preisman, S., Eldar, I. and Perel, A. The effects of epidural and spinal anesthesia on the changes in the plethysmographic signal in the lower and upper limbs, (*ESA*) A.124

Preisman, S., Shneider, A., Pfeiffer, U. and Perel, A. A comparison between various hemodynamic parameters reflecting preload during graded hemorrhage in ventilated dogs, (*ESA*) A.51

Price, M. Changes in haemodynamic variables with thiopentone, methohexitone, propofol and etomidate, (*C*) 116

Proost, J. H. *see* Plaud, B., (*ESA*) A.141

Pruett, J. K. *see* Martin, D. C. 365–367

Prys-Roberts, C. *see* Hasan, M. A. 141–144

Puhakka, K., Räsänen, J., Leijala, M. and Peltola, K. Metabolic effects of corrective surgery in infants and children with congenital heart defects 149–153

Puig, M. M. *see* Fernandez, D., (*ESA*) A.131; Fernandez, S., (*ESA*) A.119; Samsó, E., (*ESA*) A.205

Puybasset, L., Oris, B., Coriat, P., Gosgnach, M. and Viars, P. Influence of chronic angiotensin converting enzyme inhibition on systolic pressure variation during anesthetic induction, (*ESA*) A.39

Py, C., Perdrix, J. P., Baconnier, P., Eberhard, A., Fargnoli, J. M., Coppo, F. and Banssillon, V. Continuous monitoring of the ventilatory mechanics during anaesthesia & intensive care, (*ESA*) A.57

Quiney, N. F. and Allen, P. Use of lignocaine in ventricular defibrillation? (*C*) 380

Quinquis, V. *see* Benhamou, D., (*ESA*) A.120

Quintilla, R. *see* Joos, S., (*ESA*) A.130

Rabeeah, A. *see* Ahmad, R. 696–698

Radbruch, L., Grond, S., Zech, D. and Lehmann, K. A. High dose oral morphine in cancer pain management, (*ESA*) A.212

Rafferty, T. *see* Cunningham, A. J. 621–625

Ramachandra, V. *see* Bennet, J., (*ESA*) A.73

Ramos, M. *see* Riou, B., (*ESA*) A.103

Randell, T. *see* Lindgren, L. 306–310; Watanabe, H. 94–95

Raner, C., Biber, B., Lundberg, J., Martner, J. and Winsö, O. Does exogenous dopamine reverse cardiovascular depression induced by isoflurane during thoracic epidural blockade? (*ESA*) A.49

Raner, C. *see* Sundeman, H., (*ESA*) A.50

Ranieri, R. *see* Crea, M. A., (*ESA*) A.63

Räsänen, J. *see* Puhakka, K. 149–153

Rasi, V. *see* Kuitunen, A. 173–180

Rath, W. *see* Crozier, T. A. 47–53

Rauch, H., Fleischer, F., Haußmann, R., Böttiger, B. and Martin, E. Propofol/fentanyl-anesthesia in patients with highly depressed cardiac function, (*ESA*) A.30

Rauss, A. *see* Beydon, L., (*ESA*) A.4

Ravishankar, M. and Chatterjee, S. Fractional utilization of fresh gas by breathing systems without carbon dioxide absorption, (*C*) 706–707

Ravussin, P. *see* Borgeat, A. 459–461; Samaha, T., (*ESA*) A.118

Rawal, N. Organization of acute pain services—a low-cost model, (*ESA*) A.199

Rawal, N., Hallén, J., Amilon, A. and Hellstrand, P. Improvement in i.v. regional anaesthesia by re-exsanguination before surgery 280–285

Read, M. *see* Carli, F., (*ESA*) A.86

Read, M. S. and Vaughan, R. S. Preoperative drinking and gastric contents, (*C*) 701

Ready, L. B., Edwards, W. T. and Task Force on Acute Pain, (editors) *Management of Acute Pain: A Practical Guide*, (*R*) 495

Reeder, M. K., Goldman, M. D., Loh, L., Muir, A. D. and Casey, K. R. Haemodynamic effects of periodic ventilation: abolition with supplementary oxygen 119

Reeder, M. K., Goldman, M. D., Loh, L., Muir, A. D., Foëx, P., Casey, K. R. and McKenzie, P. J. Postoperative hypoxaemia after major abdominal vascular surgery 119

Reeder, M. K., Muir, A. D., Foëx, P., Goldman, M. D., Loh, L. and Smart, D. Postoperative myocardial ischaemia: temporal association with nocturnal hypoxaemia 119

Reid, J. *see* Nolan, A. 546–551

Reignier, J., Ben Ameur, M. and Ecoffey, C. Ventilation with halothane is less affected in children with laryngeal mask airway than with endotracheal tube, (*ESA*) A.162

Reilly, C. S. *see* Berthoud, M. C. 423–427; Myles, A. P., (*ARS*) 476–477P; Peacock, J. E., (*C*) 383–384

Reinhart, K. *see* Meier-Hellmann, A., (*ESA*) A.185; Spies, C., (*ESA*) A.110; (*ESA*) A.186

Reiz, S., Johansson, G., Hohner, P. and Häggmark, S. The use of the CUSUM plot for determination of myocardial ischaemia threshold during atrial pacing in patients with coronary artery disease, (*ESA*) A.24

Reiz, S., Nyström, E., Tugrul, M., Häggmark, S. and Johansson, G. Influence of cervicothoracic epidural anaesthesia (C-TEA) on left ventricular (LV) contractility—an experimental study in pigs with autonomous blockade, (*ESA*) A.52

Reiz, S. *see* Hohner, P., (*ESA*) A.26; (*ESA*) A.41; Nyström, E., (*ESA*) A.65; Österlund, B., (*ESA*) A.19; Östman, M., (*ESA*) A.22

Renkl, F. *see* Dittmann, M., (*ESA*) A.126

Revel, P. *see* Janvier, G. 186–191

Reynolds, F. Antepartum assessment for anaesthesia, (*C*) 116

Rice, A. S. C. and McMahon, S. B. Peripheral nerve damage and regional anaesthesia, (*C*) 594

Rice, A. S. C. *see* Kitching, A. J., (*C*) 703

Richards, J. *see* Beck, G. N., (*ARS*) 483P

Richardson, J. B. *see* Knapik, P., (*ESA*) A.61; (*ESA*) A.69

Richer, J.-P. *see* Le Pelley, E., (*ESA*) A.48

Rieger, A. *see* Striebel, W. H., (*ESA*) A.209; (*ESA*) A.210

Riez, S. *see* Hohner, P., (*ESA*) A.23

Riley, B. *see* Ooi, R. 17–21; 494

Rimaniol, J. M. *see* Fulgencio, J. P., (*ESA*) A.42

de los Ríos, J., Iribarren, M. J., Monedero, P., García-Pedrajas, F. and Arroyo, J. L. Modification of the renin–aldosterone axis during orthotopic liver transplantation, (*ESA*) A.75

de los Ríos, J. *see* Carrera, J., (*ESA*) A.77

Riou, B., Cavallier, S., Roy-Camille, R. and Viars, P. Preoperative autotransfusion in emergency surgery for spine trauma, (*ESA*) A.102

Riou, B., Guerrero, M., Arock, M., Ramos, M. and Viars, P. Effects of postoperative auto-transfusion in spine surgery, (*ESA*) A.103

Riou, B., Guesde, R., Jacquens, Y., Duranteau, R. and Viars, P. Fiberoptic bronchoscopy in brain dead organ donors, (*ESA*) A.80

Riou, B. *see* Duranteau, R., (*ESA*) A.148; Goarin, J. P., (*ESA*) A.193; Guesde, R., (*ESA*) A.79; Saada, M., (*ESA*) A.194

Ripart, J., Cohendy, R. and Eledjam, J.-J. The laryngeal mask and intraocular surgery, (*C*) 704

Ritter, M. *see* Faris, P. P., (*ESA*) A.101

Rittoo, D. B., Breed, N. and Pollard, B. J. Preoxygenation and Sp_{O_2} after induction of anaesthesia with propofol and fentanyl, (*ARS*) 486P

Robinson, D. L. Frequency of damaged coaxial breathing systems, (*C*) 384

Robinson, D. L. *see* Lamond, C. T., (*ESA*) A.204

Robson, S. C., Samsoon, G., Boys, R. J., Rodeck, C. and Morgan, B. Incremental spinal anaesthesia for elective Caesarean section: maternal and fetal haemodynamic effects 634–638

Rodeck, C. *see* Robson, S. C. 634–638

Rodet, L. *see* Kozak Ribbens, G., (*ESA*) A.92

Rohierse-Hohler, I. *see* Striebel, H. W., (*ESA*) A.208

Rolly, G. *see* Mergaert, C., (*ESA*) A.149; Van Bastelaere, M., (*ESA*) A.146

Romppanen, O. *see* Rorarius, M. G. F. 293–297

Rorarius, M. G. F., Suominen, P., Baer, G. A., Romppanen, O. and Tuimala, R. Diclofenac and ketoprofen for pain treatment after elective Caesarean section 293–297

Ros, H. H. *see* de Jong, J. R., (*ESA*) A.15

Rosen, M., Latto, P. and Ng, S., (editors) *Handbook of Percutaneous Central Venous Catheterisation*, 2nd Edn, (*R*) 601

Rosenbaum, S. *see* Cunningham, A. J. 621–625

Rosenberg, P. *see* Watanabe, H. 94–95

Rosenberg, P. H., Taivainen, T., Pitkänen, M. and Tuominen, M. Epidural blood patch for treatment of postdural puncture headache, (*ESA*) A.129

Rosenberg, P. H. *see* Pere, P. 276–279

Rosencher, N. *see* Vassilieff, N., (*ESA*) A.71

Rossaro, L. *see* Piccinni, P., (*ESA*) A.78

Rosso, J. *see* Liu, N., (*ESA*) A.25

Rothen, H. U., Sporre, B., Engberg, G., Wegenius, G. and Hedenstierna, G. Recruitment of atelectasis during general anaesthesia: a CT-study, (*ESA*) A.53

Rothenbühler, J. M. *see* Urwyler, A. 76–79

Rouby, J. J., Lherm, T., de Lassale, M. E., Poete, P., Bodin, L. and Viars, P. Histology aspects of pulmonary barotrauma in critically ill patients with acute respiratory failure, (*ESA*) A.181

Rouby, J. J. *see* Bodin, L., (*ESA*) A.179; (*ESA*) A.191; Kalfon, P., (*ESA*) A.182

Rouby, J.-J. *see* Saada, M., (*ESA*) A.194; Vivien, B., (*ESA*) A.183

Roulson, C. J. *see* Jones, R. D. M. 286–292

Rouvier, B. *see* Descraques, C., (*ESA*) A.127

Rowan, E. G. *see* Braga, M. F. M. 405–410

Rowbotham, D. J. *see* Appadu, B., (*ARS*) 477P; Atcheson, R., (*ARS*) 485P

Rowe, P. *see* Wolf, A. R. 654–660

Roy-Camille, R. *see* Riou, B., (*ESA*) A.102

Royston, B. D. *see* Landon, A. J. 605–611

Rue, M. *see* Fernandez, D., (*ESA*) A.131

Ruggier, R. *see* Bailey, C. R., (*ESA*) A.169

Runcie, C. J. Statistical assessment of two methods of clinical measurement, (*C*) 595

Runcie, C. J., Mackenzie, S. J., Arthur, D. S. and Morton, N. S. Comparison of recovery from anaesthesia induced in children with either propofol or thiopentone 192–195

Runciman, W. B. *see* Huang, Y. F. 326–332; 556–561

Rupreht, J. *see* Dzoljic, M., (*ESA*) A.112

Russell, I. F. Midazolam–alfentanil: an anaesthetic? An investigation using the isolated forearm technique 42–46

Russell, R. Continuous subarachnoid infusion of 0.125% bupivacaine for analgesia during labour, (*C*) 699–700

Ryan, T., Timoney, A. and Cunningham, A. J. Use of transoesophageal echocardiography to manage beta-adrenoceptor block and assess left ventricular function in a patient with phaeochromocytoma 101–103

Ryckman, J. V. *see* Whalley, D. G. 96–98

Saada, M., Riou, B., Goarin, J.-P., Rouby, J.-J., Jacquens, Y. and Viars, P. Systemic gas embolism in pulmonary contusion diagnosed by transesophageal echocardiography, (*ESA*) A.194

Saada, M. *see* Fulgencio, J. P., (*ESA*) A.42; Goarin, J. P., (*ESA*) A.193; Hohner, P., (*ESA*) A.26; Liu, N., (*ESA*) A.25; Vivien, B., (*ESA*) A.183

Sabanathan, S. *see* Berrisford, R. G. 201–204

Saich, T. *see* Jacobson, W. 522–526

Saint-Maurice, C. *see* Menigaux, C., (*ESA*) A.175

Saïssi, G. *see* Lefrant, J. Y., (*ESA*) A.18

Saitoh, Y., Toyooka, H. and Amaha, K. Recoveries of post-tetanic twitch and train-of-four responses after administration of vecuronium with different inhalation anaesthetics and neuroleptanaesthesia 402–404

Salevsky, F. C. *see* Whalley, D. G. 96–98

Salmenperä, M. *see* Kuitunen, A. 173–180

Salonen, M., Kendig, J., O'Connor, B. and Maze, M. Dexmedetomidine does not exercise its anesthetic action through GABA, (*ESA*) A.113

Samaha, T., Ravussin, P., Clacquin, C. and Ecoffey, C. Effect of esmolol *versus* lidocaine on intracranial pressure and haemodynamic responses to laryngoscopy and intubation, (*ESA*) A.118

Samama, C. M., Mazoyer, E., Bruneval, P., Bonnin, P.,

Bonneau, M., Pignaud, G., Viars, P., Caen, J. P. and Drouet, L. O. Aprotinin does not decrease surgical bleeding and could promote arterial thrombosis in the pig: a prospective randomized, blind, study, (*ESA*) A.100
Samama, M. *see* Lequeau, F., (*ESA*) A.97
Sami, K. A. *see* Ahmad, R. 696–698
Samii, K. *see* Butscher, K., (*ESA*) A.201; Dupont, H., (*ESA*) A.9; Mimoz, O., (*ESA*) A.180
Samsó, E., Murga, G., Valles, J., Gallart, L. L. and Puig, M. M. Effects of epidural clonidine on anaesthetic requirements and postoperative analgesia, (*ESA*) A.205
Samsoon, G. *see* Robson, S. C. 634–638
Sandin, R. Propofol and alfentanil mixture, (*C*) 382–383
Sandin, R. *see* Nordström, O. 368–369
Sandler, A. N. *see* Katz, J., (*C*) 378
Sansone, A. *see* Santangelo, E., (*ESA*) A.206; Savoia, G., (*ESA*) A.159
Santangelo, E., Amantea, B., Sansone, A., Savoia, G. and Sparacia, B. Safety of PCA in elderly, (*ESA*) A.206
Sapsford, D. J. *see* Munglani, R., (*ARS*) 483–484P
Sassine, A. *see* de La Coussaye, J. E., (*ESA*) A.121
Saux, P. *see* Martin, C., (*ESA*) A.20; (*ESA*) A.189
Savoia, G., Lucke, F., Sparacia, B. and Sansone, A. Blended anaesthesia in pediatric major surgery: top-up *vs* epidural continuous infusion, (*ESA*) A.159
Savoia, G. *see* Santangelo, E., (*ESA*) A.206
Saydam, G. *see* Durak, P., (*ESA*) A.96
Schäfer, H.-G. *see* Dittmann, M., (*ESA*) A.126
Schäfer, R., Gerling, W., Utschakowski, A. and Wagner, K. Influence of norepinephrine therapy on the oxygen supply and lactate extraction rate of the liver in the septic pig, (*ESA*) A.184
Schäfermeyer, H. *see* Schregel, W., (*ESA*) A.105
Scheinin, M. *see* Kuitunen, A. 173–180; Lindgren, L. 306–310
Scherer, R. U., Giebler, R. M., Schmutzler, M. J., Günnicker, F. M. and Kox, W. J. Shunt flow and caval pressure gradient during veno-venous bypass in human orthotopic liver transplantation 689–690
Schierbeck, J. *see* Koscielniak-Nielsen, Z. J., (*ESA*) A.157
Schindler, E. *see* Boldt, J. 661–665
Schiraldi, F. *see* Iannuzzi, E., (*ESA*) A.195
Schmartz, D. M. *see* Baurain, M. J., (*ESA*) A.133; (*ESA*) A.135
Schmucker, P. *see* Eleftheriadis, S., (*ESA*) A.3
Schmutzler, M. J. *see* Scherer, R. U. 689–690
Schneider, M. *see* Weiss, M. 317–321
Schoeffler, P., (editor) *Anesthésie et Analgésie en Obstétrique. Collection d'Anesthésiologie et de Réanimation*, Vol. 33, (*R*) 708
Schoeffler, P. *see* Bazin, J. E., (*ESA*) A.136
Schregel, W., Geißler, C., Bredenkötter, U. and Schäfermeyer, H. Transcranial Doppler sonography: effect of propofol and thiopental in patients with brain tumors and brain injuries, (*ESA*) A.105
Schwilden, H. and Stoeckel, H. Closed-loop feedback controlled administration of alfentanil during alfentanil–nitrous oxide anaesthesia 389–393
Scott, N. B. *see* Forbes, D., (*ESA*) A.125
Sear, J. W. Why not model physiologically? (*E*) 243–245
Seebacher, J. *see* Thirion, A.-V., (*ESA*) A.172; Thormann, F., (*ESA*) A.173
Seeberger, M. D. and Urwyler, A. Lumbovertebral syndrome after extradural blood patch, (*C*) 489
Seeberger, M. D. *see* Urwyler, A. 76–79
Sefrin, R. *see* Molter, G. 428–433
Seppälä, E. *see* Ojanen, R., (*ESA*) A.94
Sermeus, L. *see* Wiebalck, A., (*ESA*) A.90; (*ESA*) A.154
Servais, R. *see* Joos, S., (*ESA*) A.130
Servin, F. *see* Malinovsky, J.-M. 617–620
Sessler, D. I. *see* Vassilieff, N., (*ESA*) A.71
Setzis, D. *see* Skourtis, C., (*ESA*) A.36
Shachor, D. *see* Jedeiken, R., (*C*) 491–492
Sharkey, A., Gulden, R. H., Lipton, J. M. and Giesecke, A. H. Effect of radiant heat on the metabolic cost of postoperative shivering 449–450
Sharma, R. *see* Nyström, E., (*ESA*) A.65
Shaw, C. *Specialty Medical Audit* (Medical Audit Series 4), (*R*) 495
Shearer, E. S. *see* Hunter, J. M., (*C*) 238–239
Shenkman, Z., Shir, Y. and Brodsky, J. B. Perioperative management of the obese patient 349–359
Shir, Y. *see* Shenkman, Z. 349–359
Shneider, A. *see* Perel, A., (*ESA*) A.117; Preisman, S., (*ESA*) A.51
Short, T. G. *see* Aun, C. S. T. 647–653
Shorten, G. D., Ali, H. H. and Goudsouzian, N. G. Neostigmine and edrophonium antagonism of moderate neuromuscular block induced by pancuronium or tubocurarine 160–162
Simon, L. *see* Wolf, A. R. 654–660
Singelyn, F. J. *see* Van Boven, M. J., (*ESA*) A.87
Singh, P. *see* Mahajan, R. P., (*ESA*) A.68
Sipos, E. *see* Weindlmayr-Goettel, M. 579–580
Skinner, A. C. Death certification, (*C*) 112
Skourtis, C., Karalazos, L. and Setzis, D. Alternating right to left ventricular ejection; the case of occult cardiac tamponade, (*ESA*) A.36
Skoyles, J. and Pepperman, M. IVOX, (*E*) 603–604
Slade, J. M. Extradural 0.07% bupivacaine for postoperative pain, (*ARS*) 478P
Slater, R. M. *see* Lamb, J. M., (*ARS*) 478–479P
Smail, N. *see* Gosgnach, M., (*ESA*) A.21
Smart, D. *see* Reeder, M. K. 119
Smilov, I. and Borissov, B. Epidural clonidine analgesia after major gynaecological surgery, (*ESA*) A.176
Smith, D. C., Dryden, C. M. and Hume, M. A. Metabolic effects of dobutamine, (*C*) 236–237
Smith, G. Perioperative blood loss, (*C*) 493
Smith, G. *see* Erskine, R. J. 574–575; Langton, J. A. 126–130; Murphy, P. J. 131–134
Smith, I. and White, P. F. Pipecuronium-induced prolongation of vecuronium neuromuscular block 446–448
Smith, I. D. *see* Jones, R. D. M. 286–292
Smith, J. A. S. Possible venous air embolism with a new water jet dissector 466–467
Smith, M. B. *see* Gilligan, S., (*C*) 491
Smith, P. *see* Williams, O. A., (*ARS*) 479P
Snowdon, S. L. *see* Head-Rapson, A. G., (*ARS*) 488P; Parker, C. J. R. 38–41
Soini, H. *see* Ali-Melkkilä, T., (*ESA*) A.145
Soler, J. P. *see* Thormann, F., (*ESA*) A.173
Sollazzi, L. *see* Crea, M. A., (*ESA*) A.63
Sollevi, A. *see* Odeberg, S., (*ESA*) A.34
Soni, N. *see* Ooi, R. 17–21; 494
Sorbara, C. *see* Armellin, G., (*ESA*) A.104; Marcassa, A., (*ESA*) A.168
Søreide, E., Søreide, J. A., Holst-Larsen, H. and Steen, P. A. Studies of gastric content: comparison of two methods 360–362
Søreide, J. A. *see* Søreide, E. 360–362
Sparacia, B. *see* Santangelo, E., (*ESA*) A.206; Savoia, G., (*ESA*) A.159
Speer, C. P. *see* Crozier, T. A. 47–53
Spencer, A., Farhat, F., Bourgain, J.-L. and Jayr, C. Postoperative hypoxaemia: comparison of epidural and patient controlled analgesia, (*ESA*) A.207
Spies, C., Kraemer, S., Heil, T., Neumann, T. and Reinhart, K. EEG-monitoring during defibrillator-implantation: effects of repetitive cerebral ischemia on electric brain activity, (*ESA*) A.110
Spies, C., Witt, I., Walensky, C., Hannemann, L. and Reinhart, K. Influence of N-acetylcysteine on O_2 consumption and gastric intramucosal pH in septic patients, (*ESA*) A.186
Spies, C. *see* Heil, T., (*ESA*) A.88
Spoelder, E. M. *see* Wagemans, M. F. M., (*ESA*) A.213
Sporre, B. *see* Rothen, H. U., (*ESA*) A.53
Stacca, R. *see* Foppoli, R., (*ESA*) A.132
Stanley, I. J. *see* Wolf, A. R. 654–660
Steen, P. A. *see* Søreide, E. 360–362
Stefanou, P. *see* Georgiou, L., (*ESA*) A.60
Steinbereithner, K. *see* Weindlmayr-Goettel, M. 579–580
Stellin, G. *see* Marcassa, A., (*ESA*) A.168
Stemp, L. I. *see* Alderson, P. J. 145–148
Stens Pedersen, H. L. *see* Koscielniak-Nielsen, Z. J., (*ESA*) A.157
Stevens, J. J. W. M., Griffin, R. M. and Stow, P. J. Prolonged use of isoflurane in a patient with tetanus 107–109
Stewart, A. D. *see* Ball, S. P. 70–75
Stoeckel, H. *see* Schwilden, H. 389–393
Stott, D. G. and Wallbank, W. A. Electrode burns during local hyperthermia 370–371
Stow, P. J. *see* Stevens, J. J. W. M. 107–109
Strauß, J. M. and Hausdörfer, J. Accumulation of acetone in blood during long-term anaesthesia with closed systems 363–364
Stride, P. C. Lumbovertebral syndrome after extradural blood patch, (*C*) 489
Striebel, H. W., Krämer, J., Luhmann, I., Rohierse-Hohler, I. and Triltsch, A. Pharmacokinetics of intranasal fentanyl, (*ESA*) A.208
Striebel, W. H., Pommerening, J., Rieger, A. and Brummer, G. Intranasal fentanyl for postoperative pain management in an unselected population, (*ESA*) A.209
Striebel, W. H., Wessel, A., Rieger, A. and Boerger, N. Intranasal fentanyl for breakthrough cancer pain or incident pain, (*ESA*) A.210

Strimbu, M. *see* Guirimand, F., (*ESA*) A.116
Strunin, L. How long should patients fast before surgery? Time for new guidelines, (*E*) 1–3; Preoperative drinking and gastric contents, (*C*) 702
Strunin, L. *see* Elliott, R. H. 339–348; Palayiwa, E., (*ARS*) 485P
Sundeman, H., Biber, B., Winsö, S., Martner, J. and Raner, C. Local *versus* neurogenic vasodilator effects of desflurane and isoflurane in the small intestine, (*ESA*) A.50
Sung, R. Y. T. *see* Aun, C. S. T. 647–653
Suominen, P. *see* Rorarius, M. G. F. 293–297
Suter, P. M. *see* Artigas, A., (*R*) 117
Svanström, M., Johansson, G. and Bålfors, E. Mechanisms of ECG changes during Caesarean section (CS)—a hypothesis, (*ESA*) A.177
Svenberg, T. *see* Odeberg, S., (*ESA*) A.34

Taivainen, T. *see* Meretoja, O. A., (*ESA*) A.140; Rosenberg, P. H., (*ESA*) A.129
Takada, K., Murai, T., Kanayama, T. and Koshikawa, N. Effects of midazolam and flunitrazepam on the release of dopamine from rat striatum measured by *in vivo* microdialysis 181–185
Tam, Y. H. *see* Tan, I. K. S. 267–272
Tan, I. K. S., Bhatt, S. B., Tam, Y. H. and Oh, T. E. Effects of PEEP on dynamic hyperinflation in patients with airflow limitation 267–272
Tan, P. *see* Gin, T. 311–316
Tashiro, C. *see* Tomi, K. 684–686
Task Force on Acute Pain *see* Ready, L. B., (*R*) 495
Taylor, I. N. and Kenny, G. N. C. Propofol and alfentanil mixture, (*C*) 383
Taylor, P. M. Veterinary use of "Xylocaine" spray, (*C*) 113
Teien, D. *see* Östman, M., (*ESA*) A.22
Teillac, P. *see* Jacob, L., (*ESA*) A.85
Testa, S. *see* Malinovsky, J.-M. 617–620
Thirion, A.-V., Henry, M., Cornet, A., Seebacher, J. and Viars, P. Spinal anesthesia for C section: addition of phenylephrine to ephedrine for prevention of maternal hypotension, (*ESA*) A.172
Thomann, P. *see* Geisslinger, G. 666–671
Thomas, D. *see* Lacoste, L., (*ESA*) A.67
Thomas, T. A. *see* Hasan, M. A. 141–144
Thommesen, L. *see* Dale, O. 454–455
Thormann, F., Henry, M., Soler, J. P., Seebacher, J. and Viars, P. Headache—new needles and spinal anaesthesia for C. section, (*ESA*) A.173
Thornton, C. and Newton, D. E. F. Brain partial pressures of isoflurane and nitrous oxide, (*C*) 705
Tighe, S. Q. M. Use of the laryngeal mask and face mask by inexperienced personnel, (*C*) 114–115
Timoney, A. *see* Ryan, T. 101–103
Timour, Q. *see* Freysz, M., (*ESA*) A.46
Toftdahl, D. B. *see* Crawford, M. E. 642–646
Tolley, P., Watts, A. and Hickman, J. Use of the laryngeal mask and face mask by inexperienced personnel, (*C*) 115
Tomi, K., Mashimo, T., Tashiro, C., Yagi, M., Pak, M., Nishimura, S., Nishimura, M. and Yoshiya, I. Alterations in pain threshold and psychomotor response associated with subanaesthetic concentrations of inhalation anaesthetics in humans 684–686
Tomlinson, B. *see* Oh, T. E., (*C*) 237–238
Toyooka, H. *see* Saitoh, Y. 402–404
Treiber, H. S. *see* Gauss, A. 591–592
Tricoche, R. *see* Le Pelley, E., (*ESA*) A.48
Triltsch, A. *see* Striebel, H. W., (*ESA*) A.208
Tripepi, A. *see* Piccinni, P., (*ESA*) A.78
Tronson, M. *see* Hatfield, A., (*R*) 709
Tryba, M. *see* Kulka, P. J., (*ESA*) A.143
Tsai, Y.-C., Lai, Y.-Y. and Chang, C.-L. Comparison of the effect of EMLA cream, subcutaneous ring anaesthesia and a double cuff technique in the prevention of tourniquet pain 394–396
Tsiotou, A. *see* Georgiou, L., (*ESA*) A.60
Tugrul, M. *see* Reiz, S., (*ESA*) A.52
Tuimala, R. *see* Rorarius, M. G. F. 293–297
Tunstall, M. E. *see* Levy, D. M., (*C*) 701–702
Tuominen, M. *see* Pere, P. 276–279; Rosenberg, P. H., (*ESA*) A.129
Türkan, H. *see* Bayhan, N., (*ESA*) A.123
Türkmen, A. *see* Durak, P., (*ESA*) A.96
Turner, G. *see* Cooper, D. W. 503–507
Turner, J. *see* Cunningham, A. J. 621–625

Uncles, D. R. and Carrie, L. E. S. Antepartum assessment
Upton, R. N. and Huang, Y. F. Influence of cardiac output, injection time and injection volume on the initial mixing of drugs with venous blood after i.v. bolus administration to sheep 333–338
Upton, R. N. *see* Huang, Y. F. 326–332; 556–561
Urwyler, A., Censier, K., Seeberger, M. D., Rothenbühler, J. M., Kaufmann, M. A. and Drewe, J. *In vitro* effect of ephedrine, adrenaline, noradrenaline and isoprenaline on halothane-induced contractures in skeletal muscle from patients potentially susceptible to malignant hyperthermia 76–79
Urwyler, A. *see* Seeberger, M. D., (*C*) 489
Utschakowski, A. *see* Schäfer, R., (*ESA*) A.184

Valles, J. *see* Samsó, E., (*ESA*) A.205
Vallet, T. *see* Lacoste, L., (*ESA*) A.67
Vanacker, B. *see* Wiebalck, A., (*ESA*) A.90; (*ESA*) A.154
Van Aken, H. *see* Baudot, J., (*ESA*) A.170; Blockmans, D., (*ESA*) A.40; Wiebalck, A., (*ESA*) A.90; (*ESA*) A.154
Van Bastelaere, M., Rolly, G. and Van Peer, A. Pharmacokinetic behaviour of transdermal fentanyl, (*ESA*) A.146
Van Boven, M. J., Pendeville, P. E. and Singelyn, F. J. Glycine and its metabolites during and after intrauterine YAG laser surgery, (*ESA*) A.87
Vandekerckhove, T. *see* De Deyne, C., (*ESA*) A.106
Van Elstraete, A. C., Pennant, J. H., Gajraj, N. M. and Victory, R. A. Tracheal tube cuff inflation as an aid to blind nasotracheal intubation 691–693
Van Hemelrijck, J. *see* Blockmans, D., (*ESA*) A.40
Vanner, R. G. Regurgitation and the laryngeal mask airway, (*C*) 380–381
Van Obbergh, L. J., Zeippen, B., Muller, G. and Veyckemans, F. Relationship between arterial $P\text{CO}_2$ (Pa_{CO_2}) and end tidal CO_2 (ETCO_2) recorded through a laryngeal mask (LMA) in children breathing spontaneously, (*ESA*) A.164
Van Peer, A. *see* Van Bastelaere, M., (*ESA*) A.146
Vapaatalo, H. *see* Ojanen, R., (*ESA*) A.94
Vasdev, G. M. S. and Leicht, C. H. Extradural abscess in the postpartum period, (*C*) 703–704
Vassilieff, N., Rosencher, N., Sessler, D. I., Conseiller, C. T. and Lienhart, A. Effect of premedication with nifedipine on intraoperative hypothermia, (*ESA*) A.71
Vaughan, R. S. Double-lumen tubes, (*E*) 497–498
Vaughan, R. S. and Cobley, M. The airway decides the anaesthetic approach before tracheal intubation, (*C*) 600
Vaughan, R. S. *see* Cobley, M. 576–578; Read, M. S., (*C*) 701
Venkat, N. *see* Hanna, M. H. 511–514
Verborgh, C. *see* Ivens, D., (*ESA*) A.17
Vercher, J. L. *see* Paut, O., (*ESA*) A.10
Vereczkey, Z., Babik, B., Fogas, J., Méray, J. and Baltás, B. Abdominal wall retraction may decrease anaesthesiological risks of laparoscopic cholecystectomy, (*ESA*) A.64
Verghese, C. *see* Walker, M. B., (*C*) 114
Vernon, D. *see* Crawford, M. 419–422
Versichelen, L. *see* Mergaert, C., (*ESA*) A.149
Vertommen, J. D. *see* Baudot, J., (*ESA*) A.170
Veyckemans, F. *see* Van Obbergh, L. J., (*ESA*) A.164
Viars, P. *see* Beaussier, M., (*ESA*) A.37; Bodin, L., (*ESA*) A.179; (*ESA*) A.191; Coriat, P., (*ESA*) A.38; Delayance, S., (*ESA*) A.45; Duranteau, R., (*ESA*) A.148; Fellahi, J. L., (*ESA*) A.44; Goarin, J. P., (*ESA*) A.193; Gosgnach, M., (*ESA*) A.5; (*ESA*) A.6; (*ESA*) A.21; Guesde, R., (*ESA*) A.79; Kalfon, P., (*ESA*) A.182; Mouquet, C., (*ESA*) A.82; (*ESA*) A.83; (*ESA*) A.84; Puybasset, L., (*ESA*) A.39; Riou, B., (*ESA*) A.80; (*ESA*) A.102; (*ESA*) A.103; Rouby, J. J., (*ESA*) A.181; Saada, M., (*ESA*) A.194; Samama, C. M., (*ESA*) A.100; Thirion, A.-V., (*ESA*) A.172; Thormann, F., (*ESA*) A.173; Vivien, B., (*ESA*) A.183
Vickers, R. J. and May, A. E. Long-term backache after extradural or general anaesthesia for manual removal of placenta: preliminary report 214–215
Victory, R. A. *see* Van Elstraete, A. C. 691–693
Vinelli, M. *see* Degasperi, D., (*ESA*) A.59
Virkkilä, M. *see* Ali-Melkkilä, T., (*ESA*) A.145
Viviand, X., Guidon-Attali, C., Lacarelle, B., Martin, C. and François, G. Determination of a pharmacokinetic model for propofol induction of anaesthesia, (*ESA*) A.150
Viviand, X. *see* Albanese, J., (*ESA*) A.107
Vivien, B., Mourgeon, E., Saada, M., Goarin, J.-P., Rouby, J.-J. and Viars, P. Evaluation of cardiac function in ICU: right heart catheterization *vs* transesophageal

Wagemans, M. F. M., Zuurmond, W. W. A., Spoelder, E. M. and de Lange, J. J. Intrathecal pain relief in terminally ill cancer patients at home, *(ESA)* A.213

Wagener, G. *see* Fruhstorfer, H. 167–172

Wagner, K. *see* Schäfer, R., *(ESA)* A.184

Walensky, C. *see* Spies, C., *(ESA)* A.186

Walker, D. R. *see* Gupta, N. K., *(C)* 699

Walker, M. B., Goodwin, A. P. L. and Verghese, C. Use of the laryngeal mask and face mask by inexperienced personnel, *(C)* 114

Wallbank, W. A. *see* Stott, D. G. 370–371

Walsh, G. *see* Joshi, G. P. 87–88

Wang, C., Koutsoukou-Dritsopoulou, A., Chakrabarti, M. K., Holdcroft, A. and Whitwam, J. G. Differential effects of alfentanil, fentanyl, pethidine and lignocaine administered intrathecally on nociceptive responses evoked by low and high frequency stimulation of somatic nerves 63–69

Ward, C. S. *see* Davey, A., *(R)* 240

Wargnier, J. P. *see* Gentili, M. E., *(C)* 594

Watanabe, H., Lindgren, L., Rosenberg, P. and Randell, T. Glycopyrronium prolongs topical anaesthesia of oral mucosa and enhances absorption of lignocaine 94–95

Watson, N. A., Munday, I. T. and Jones, R. M. Relative efficacy and potency of nalmefene, a long-acting opioid antagonist, *(ARS)* 479P

Watt, T., Faragher, B., Withers, D. J., England, R. E., Martin, D. F. and Campbell, I. T. Ultrasound measurement of muscle thickness in the estimation of fat free mass, *(ARS)* 477P

Watts, A. *see* Tolley, P., *(C)* 115

Webb, A. *see* Mythen, M., *(ESA)* A.29

Wegenius, G. *see* Rothen, H. U., *(ESA)* A.53

Weidmann, G. *see* Biro, P., *(ESA)* A.156

Weindlmayr-Goettel, M., Gilly, H., Sipos, E. and Steinbereithner, K. Lipid solubility of pancuronium and vecuronium determined by n-octanol/water partitioning 579–580

Weiss, M., Mirow, N., Birkhahn, A., Schneider, M. and Wernet, P. Benzodiazepines and their solvents influence neutrophil granulocyte function 317–321

Weisz, M. T. *see* Plastow, S. E., *(C)* 492

Wells, J. C. D. and Woolf, C. J., (editors) *British Medical Bulletin: A Series of Expert Reviews. Pain, Mechanisms and Management*, *(R)* 495

Wenker, O. The part of rescue helicopters in large accidents and disasters, *(ESA)* A.197

Wenngren, B.-I. *see* Nyström, E., *(ESA)* A.65

Wernet, P. *see* Weiss, M. 317–321

Wertz, E. Does etomidate cause haemolysis? *(C)* 490–491

Wessel, A. *see* Striebel, W. H., *(ESA)* A.210

Weyandt, D. *see* Meier-Hellmann, A., *(ESA)* A.185

Whalley, D. G., Salevsky, F. C. and Ryckman, J. V. Haemodynamic and metabolic consequences of aortic occlusion during abdominal aortic surgery 96–98

White, D. C. *see* Landon, A. J. 605–611

White, P. F. *see* Smith, I. 446–448

Whiteley, S. M. *see* Ogilvy, A. J., *(ARS)* 476P

Whitwam, J. G. *see* Wang, C. 63–69

Wiebalck, A., Vanacker, B., Van Aken, H., Sermeus, L., Bouillon, R. and Amery, A. Adrenocortical function: a clinical comparison of Etomidat-Lipuro® and Hypnomidate®, *(ESA)* A.90; Quality of induction: a clinical comparison of Etomidat-Lipuro® and Hypnomidate®, *(ESA)* A.154

Wierda, J. M. K. H. *see* Cooper, R., *(ARS)* 482P; Plaud, B., *(ESA)* A.141

Wiesemes, R., Klement, W., Novotny, G. E. K. and Lipfert, P. *In vivo* determination of concentration–effect curves of local anaesthetics in man 552–555

Wilder-Smith, O. H. G. *see* Borgeat, A. 459–461

Wildsmith, J. A. W. Extradural abscess after central nerve block, *(E)* 387–388; Face masks and spinal anaesthesia, *(C)* 239

Wildsmith, J. A. W. and McClure, J. H. Aspirin, bleeding time and central neural block, *(C)* 112

Wildsmith, J. A. W. *see* McClure, J. H., *(R)* 239; McCrae, A. F. 672–680

Wilkinson, D. J. Pain on i.v. injection of metoclopramide, *(C)* 239

Willatts, S. M. and Winter, R. J., (editors) *Principles and Protocols in Intensive Care*, *(R)* 239

Willer, J. C. *see* Guirimand, F., *(ESA)* A.116

Williams, E. L. Changes in haemodynamic variables with thiopentone, methohexitone, propofol and etomidate, *(C)* 115

Williams, O. A., Clarke, F. L., Harris, R. W., Smith, P. and Peacock, J. E. Addition of droperidol to patient-controlled analgesia: effect on nausea and vomiting, *(ARS)* 479P

Williams, P. J. and Bailey, P. M. Comparison of the reinforced laryngeal mask airway and tracheal intubation for adenotonsillectomy 30–33

Williamson, R. The airway decides the anaesthetic approach before tracheal intubation, *(C)* 600

Willis, B. A. *see* Cobley, M. 576–578

Willis, W., (editor) *Hyperalgesia and Allodynia*, *(R)* 385

Wilson, I. G. The laryngeal mask airway in paediatric practice, *(E)* 124–125

Winckler, C. *see* Moritz, F. 451–453

Winnock, S. *see* Janvier, G. 186–191

Winsö, O. *see* Raner, C., *(ESA)* A.49

Winsö, S. *see* Sundeman, H., *(ESA)* A.50

Winter, R. J. *see* Willatts, S. M., *(R)* 239

Winyard, J. *see* Palayiwa, E., *(ARS)* 485P

Winyard, J. A. *see* Nolan, K. M. 440–442

Withers, D. J. *see* Watt, T., *(ARS)* 477P

Witt, I. *see* Spies, C., *(ESA)* A.186

Wolf, A. R., Eyres, R. L., Laussen, P. C., Edwards, J., Stanley, I. J., Rowe, P. and Simon, L. Effect of extradural analgesia on stress responses to abdominal surgery in infants 654–660

Wolf, A. R. and Hughes, D. Pain relief for infants undergoing abdominal surgery: comparison of infusions of i.v. morphine and extradural bupivacaine 10–16

Wood, A. J. *see* Ooi, L. G. 104–106

Wood, R. A. *see* Arnold, C. 118

Woolf, C. J. *see* Wells, J. C. D., *(R)* 495

Wuttke, W. *see* Crozier, T. A. 47–53

Yagi, M. *see* Tomi, K. 684–686

Yau, G. *see* Gin, T. 311–316

Yli-Hankala, A., Lindgren, L., Porkkala, T. and Jäntti, V. Nitrous oxide-mediated activation of the EEG during isoflurane anaesthesia in patients 54–57

Yli-Hankala, A. *see* Kirvelä, M., *(ESA)* A.81; Lindgren, L. 306–310

Yoldi, J. I. *see* Martínez Urionabarrenetxea, K., *(ESA)* A.187; Pérez Arancón, J. L., *(ESA)* A.188

Yoshiya, I. *see* Tomi, K. 684–686

Young, J. D. and McQuillan, P. Comparison of thoracic electrical bioimpedance and thermodilution for the measurement of cardiac index in patients with severe sepsis 58–62

Zaouk, G., Gilbart, E., Dubois, A., Jacobs, D. and Balatoni, E. Alizapride does reduce pain on injection of propofol: comparison with lidocaine, *(ESA)* A.11

Zapol, W. M. *see* Artigas, A., *(R)* 117

Zbinden, A. M. *see* Petersen-Felix, S., *(C)* 704–705

Zech, D. *see* Radbruch, L., *(ESA)* A.212

Zeippen, B. *see* Van Obbergh, L. J., *(ESA)* A.164

Zilkha, T. R. *see* Hanna, M. H. 511–514

Zouaoui, Z. *see* Bodin, L., *(ESA)* A.179

Zuurmond, W. W. A. *see* Wagemans, M. F. M., *(ESA)* A.213

SUBJECT INDEX

ABC of Transfusion, 2nd Edn, Contreras, M., (editor), (*R*) 495

Acid–base equilibrium, Changes in blood lactate, total body oxygen delivery and consumption during liver transplantation, Carrera, J., *et al.*, (*ESA*) A.77

Acid–base equilibrium, metabolic acidosis, Acute haemodynamic effect of sodium bicarbonate in canine respiratory or metabolic acidosis, Nishikawa, T. 196–200

——, Haemodynamic and metabolic consequences of aortic occlusion during abdominal aortic surgery, Whalley, D. G., *et al.* 96–98

Acid–base equilibrium, pH, Measurement of sigmoid intramural pH during orthotopic liver transplantation, Auroy, Y., *et al.*, (*ESA*) A.76

Acid–base equilibrium, respiratory acidosis, Acute haemodynamic effect of sodium bicarbonate in canine respiratory or metabolic acidosis, Nishikawa, T. 196–200

——, An alternative method of increasing $P\text{CO}_2$ using apnoea and continuous positive airway pressure, Karlsten, R., *et al.* 411–413

Adductor pollicis, Anq 9040: effect of twice the ED$_{95}$ dose, Munday, I. T., *et al.*, (*ARS*) 480P

——, Can repetition of high frequencies stimuli alter the value of 50 and 100 Hz tetanic fade during vecuronium induced neuromuscular blockade? Baurain, M. J., *et al.*, (*ESA*) A.135

——, Comparison of the onset of depolarizing *vs* non-depolarizing block after early tourniquet release in the isolated forearm, Hood, J. R., *et al.*, (*ARS*) 480P

——, Concentration–effect relationship at the vocal cords and the adductor pollicis following rocuronium administration, Plaud, B., *et al.*, (*ESA*) A.141

——, Effect of isometric thumb preload on the evoked compound muscle action potential, Kalli, I. 92–93

——, Monitoring the onset of neuromuscular blockade at the orbicularis oculi can predict good intubating conditions when using 2 × ED$_{95}$ of atracurium, Debaene, B., *et al.*, (*ESA*) A.142

——, Potency estimation of mivacurium: comparison of two different modes of nerve stimulation, Maddineni, V. R., *et al.* 694–695

——, Recovery of atracurium and vecuronium neuromuscular block in the isolated forearm, Law Min, J.-C., *et al.*, (*ARS*) 480–481P

——, Tetanic fade during recovery from vecuronium block: comparison of systemic and isolated forearm administration, Campkin, N. T. A., *et al.* 581–582

Adult Respiratory Distress Syndrome, Artigas, A., *et al.*, (editors), (*R*) 117

Age factors, An investigation into the effect of passive and active cutaneous warming devices on intraoperative body temperature in elderly patients, Bennet, J., *et al.*, (*ESA*) A.73

——, Anesthesia for patients ⩾ 90 years of age in emergency hip surgery, Eleftheriadis, S., *et al.*, (*ESA*) A.3

——, Comparison of infusion rates of three i.v. anaesthetic agents for induction in elderly patients, Berthoud, M. C., *et al.* 423–427

——, Different rates of injection of propofol, Goodman, N. W., (*C*) 383

——, Different rates of injection of propofol, Peacock, J. E., *et al.*, (*C*) 383–384

——, Effect of age, gender and anaesthetic technique on the pharmacodynamics of atracurium, Parker, C. J. R., *et al.* 38–41

——, Effect of age on the sensitivity of upper airway reflexes, Erskine, R. J., *et al.* 574–575

——, Effectiveness of core warming on net transfer of body heat across the skin, Kulkarni, P., *et al.*, (*ESA*) A.70

——, Fresh gas requirements of an enclosed afferent reservoir breathing system in anaesthetized, spontaneously breathing adults, Barrie, J. R., *et al.* 468–470

——, Incidence of post dural puncture headache in young adults by the use of the Sprötte needle: 300 patients, Descraques, C., *et al.*, (*ESA*) A.127

——, Ketamine does not prevent hypotension caused by induction of anaesthesia with propofol in elderly patients, Blockmans, D., *et al.*, (*ESA*) A.40

——, Lung function after vecuronium pretreatment in elderly patients, Mahajan, R. P., *et al.*, (*ARS*) 482–483P

——, Minimum alveolar concentration of sevoflurane in elderly patients, Nakajima, R., *et al.* 273–275

——, Safety of PCA in elderly, Santangelo, E., *et al.*, (*ESA*) A.206

——, Subarachnoid anaesthesia (SAA) and postoperative analgesia with bupivacaine (BV) plus fentanyl (FN) in geriatric patients, Fernandez, D., *et al.*, (*ESA*) A.131

——, The pharmacokinetics of rocuronium in pediatric patients: a pooled data analysis, Meistelman, C., *et al.*, (*ESA*) A.138

Airway, aerosol penetration, Penetration of an aerosol, produced by film atomization, through the carinal bifurcation, Inglis, T. J. J., *et al.* 527–531

Airway, anatomy, A new clinical score to predict difficult intubation, Arné, J., *et al.*, (*ESA*) A.1

——, Mathematical analysis of the upper respiratory tract from an anthropometric study, Janvier, G., *et al.* 186–191

Airway, infections, A new clinical score to predict difficult intubation, Arné, J., *et al.*, (*ESA*) A.1

——, Penetration of an aerosol, produced by film atomization, through the carinal bifurcation, Inglis, T. J. J., *et al.* 527–531

Airway, mucosa, Glycopyrronium prolongs topical anaesthesia of oral mucosa and enhances absorption of lignocaine, Watanabe, H., *et al.* 94–95

Airway, obstruction, Effects of PEEP on dynamic hyperinflation in patients with airflow limitation, Tan, I. K. S., *et al.* 267–272

——, The airway decides the anaesthetic approach before tracheal intubation, Vaughan, R. S., *et al.*, (*C*) 600

——, The airway decides the anaesthetic approach before tracheal intubation, Williamson, R., (*C*) 600

Airway, patency, Continuous spirometry: an aid in the intraoperative respiratory monitoring—case reports, Bardoczky, G., *et al.*, (*ESA*) A.55

Airway, pressure, Pressure exerted by the laryngeal mask airway cuff upon the pharyngeal mucosa, Marjot, R. 25–29

Airway, reflexes, Effect of age on the sensitivity of upper airway reflexes, Erskine, R. J., *et al.* 574–575

——, Effect of oral diazepam on the sensitivity of upper airway reflexes, Murphy, P. J., *et al.* 131–134

——, Effect of stopping smoking on upper airway reflexes, Erskine, R. J., *et al.*, (*ARS*) 478P

——, Measurement of the sensitivity of upper airway reflexes, Langton, J. A., *et al.* 126–130

——, Upper airway reflexes, Drummond, G. B., (*E*) 121–123

Alcohol, Delayed presentation of an extradural abscess in a patient with alcohol abuse, Nordström, O., *et al.* 368–369

Alcohol, withdrawal, Carbohydrate deficient transferrin: a new copredictor of alcoholism related postoperative complications? Heil, T., *et al.*, (*ESA*) A.88

Anaesthesia, audit, Adequate pain relief with epidural analgesia during labor: why are women still dissatisified? Hamza, J., *et al.*, (*ESA*) A.171

——, An audit of the incidence and costs associated with post operative nausea and vomiting (PONV) following major gynaecological surgery in an inpatient population, Morris, R. W., *et al.*, (*ESA*) A.2

——, Editorial II—the National Confidential Enquiry into Perioperative Deaths, Lunn, J. N., *et al.*, (*C*) 382

Anaesthesia, day-case, Comparison of alfentanil with suxamethonium in facilitating nasotracheal intubation in day-case anaesthesia, Alcock, R., *et al.* 34–37

——, Comparison of midazolam with propofol for sedation in outpatient bronchoscopy, Crawford, M., *et al.* 419–422

——, Comparison of recovery from anaesthesia induced in children with either propofol or thiopentone, Runcie, C. J., *et al.* 192–195

——, Propofol for tracheal intubation in paediatric outpatient anaesthesia, Montasser, A. M., (*ESA*) A.161

——, Use of alfentanil with propofol for nasotracheal intubation without neuromuscular block, Coghlan, S. F. E., *et al.* 89–91

Anaesthesia, dental, Comparison of alfentanil with suxamethonium in facilitating nasotracheal intubation in day-case anaesthesia, Alcock, R., *et al.* 34–37

Anaesthesia, depth, Validation of coherent frequency of the EEG as a measure of consciousness during anaesthesia, Munglani, R., *et al.*, (*ARS*) 483–484P

Anaesthesia, general, Fresh gas requirements of an enclosed afferent reservoir breathing system in anaesthetized, spontaneously breathing adults, Barrie, J. R., *et al.* 468–470

——, Hypoxic events after general anaesthesia in the recovery room, Degasperi, D., *et al.*, (*ESA*) A.59

——, Long-term backache after extradural or general anaesthesia for manual removal of placenta: preliminary report, Vickers, R. J., *et al.* 214–215

——, Metabolic effects of propofol and flunitrazepam given for sedation after aortic surgery, Moritz, F., *et al.* 451–453

——, Recruitment of atelectasis during general anaesthesia: a CT-study, Rothen, H. U., *et al.*, (*ESA*) A.53

——, Studies of gastric content: comparison of two methods, Søreide, E., *et al.* 360–362

Anaesthesia, geriatric, Anesthesia for patients $\geq$ 90 years of age in emergency hip surgery, Eleftheriadis, S., *et al.*, (*ESA*) A.3

——, Fentanyl or buprenorphine side effects in spinal anaesthesia, Foppoli, R., *et al.*, (*ESA*) A.132

——, Ketamine does not prevent hypotension caused by induction of anaesthesia with propofol in elderly patients, Blockmans, D., *et al.*, (*ESA*) A.40

——, Minimum alveolar concentration of sevoflurane in elderly patients, Nakajima, R., *et al.* 273–275

——, Subarachnoid anaesthesia (SAA) and postoperative analgesia with bupivacaine (BV) plus fentanyl (FN) in geriatric patients, Fernandez, D., *et al.*, (*ESA*) A.131

Anaesthesia, neurosurgical, Adrenaline-induced hypotension in neurosurgery, Phillips, S., *et al.* 687–688

——, Effect of esmolol *versus* lidocaine on intracranial pressure and haemodynamic responses to laryngoscopy and intubation, Samaha, T., *et al.*, (*ESA*) A.118

Anaesthesia, obstetric, A continuous subdural block, Collier, C. B., *et al.* 462–465

——, Addition of droperidol to patient-controlled analgesia: effect on nausea and vomiting, Williams, O. A., *et al.*, (*ARS*) 479P

——, Antepartum assessment for anaesthesia, Cody, M., *et al.*, (*C*) 116

——, Antepartum assessment for anaesthesia, Reynolds, F., (*C*) 116

——, Antepartum assessment for anaesthesia, Uncles, D. R., *et al.*, (*C*) 116

——, Best Quincke point needle for Caesarean section, Lyons, G., (*ESA*) A.174

——, Continuous subarachnoid infusion of 0.125% bupivacaine for analgesia during labour, McHale, S., *et al.*, (*C*) 701

——, Continuous subarachnoid infusion of 0.125% bupivacaine for analgesia during labour, Russell, R., (*C*) 699–700

——, Diclofenac and ketoprofen for pain treatment after elective Caesarean section, Rorarius, M. G. F., *et al.* 293–297

——, Effects of etomidate on the adrenocortical and metabolic adaptation of the neonate, Crozier, T. A., *et al.* 47–53

——, Extradural abscess in the postpartum period, Kitching, A. J., *et al.*, (*C*) 703

——, Extradural abscess in the postpartum period, Ngan Kee, W. D., (*C*) 704

——, Extradural abscess in the postpartum period, Vasdev, G. M. S., *et al.*, (*C*) 703–704

——, Headache—new needles and spinal anaesthesia for C. section, Thormann, F., *et al.*, (*ESA*) A.173

——, Incremental spinal anaesthesia for elective Caesarean section: maternal and fetal haemodynamic effects, Robson, S. C., *et al.* 634–638

——, Intermittent *vs* continuous extradural infusion of bupivacaine during labour, Eddleston, J. M., (*C*) 490

——, Intermittent *vs* continuous extradural infusion of bupivacaine during labour, Laishley, R. S., (*C*) 490

——, Long-term backache after extradural or general anaesthesia for manual removal of placenta: preliminary report, Vickers, R. J., *et al.* 214–215

——, Mechanisms of ECG changes during Caesarean section (CS)—a hypothesis, Svanström, M., *et al.*, (*ESA*) A.177

——, Plasma catecholamines and neonatal condition after induction of anaesthesia with propofol or thiopentone at Caesarean section, Gin, T., *et al.* 311–316

——, Preoperative drinking and gastric contents, Levy, D. M., *et al.*, (*C*) 701–702

——, Spinal anesthesia for C section: addition of phenylephrine to ephedrine for prevention of maternal hypotension, Thirion, A.-V., *et al.*, (*ESA*) A.172

——, Spread of spinal anaesthesia for Caesarean section in singleton and twin pregnancies, Jawan, B., *et al.* 639–641

Anaesthesia, otolaryngological, Comparison of the reinforced laryngeal mask airway and tracheal intubation for adenotonsillectomy, Williams, P. J., *et al.* 30–33

Anaesthesia, paediatric, A bifurcated endobronchial tube in the management of laryngotracheo-oesophageal cleft repair, Ahmad, R., *et al.* 696–698

——, Blended anaesthesia in pediatric major surgery: top-up *vs* epidural continuous infusion, Savoia, G., *et al.*, (*ESA*) A.159

——, Cardiovascular effects of i.v. induction in children: comparison between propofol and thiopentone, Aun, C. S. T., *et al.* 647–653

——, Clonidine in paediatric caudal anaesthesia, Jamali, S., *et al.*, (*ESA*) A.160

——, Comparison of recovery from anaesthesia induced in children with either propofol or thiopentone, Runcie, C. J., *et al.* 192–195

——, Continuous monitoring of Sp_{O_2} during total intravenous anaesthesia with ketamine and spontaneous ventilation, Joly, L.-M., *et al.*, (*ESA*) A.58

——, I.v. anaesthesia with propofol using a target-controlled infusion system: comparison with inhalation anaesthesia for general surgical procedures in children, Doyle, E., *et al.* 542–555

——, Pharmacokinetics of flumazenil and midazolam, Jones, R. D. M., *et al.* 286–292

——, Plasma concentrations of midazolam after i.v., nasal or rectal administration in children, Malinovsky, J.-M., *et al.* 617–620

——, Propofol for tracheal intubation in paediatric outpatient anaesthesia, Montasser, A. M., (*ESA*) A.161

——, Relationship between arterial Pco$_2$ (Pa_{CO_2}) and end tidal CO$_2$ (ETco$_2$) recorded through a laryngeal mask (LMA) in children breathing spontaneously, Van Obbergh, L. J., *et al.*, (*ESA*) A.164

——, The laryngeal mask airway in paediatric practice, Wilson, I. G., (*E*) 124–125

——, Use of ultrasound to evaluate internal jugular vein anatomy and to facilitate central venous cannulation in paediatric patients, Alderson, P. J., *et al.* 145–148

——, Ventilation with halothane is less affected in children with laryngeal mask airway than with endotracheal tube, Reignier, J., *et al.*, (*ESA*) A.162

——, Ventilatory effects of morphine, pethidine and methadone in children, Hamunen, K. 414–418

——, Volume replacement with hydroxyethyl starch solution in children, Boldt, J., *et al.* 661–665

Anaesthesia Review 9, Kaufman, L., (editor), (*R*) 385

Anaesthesia, veterinary, Veterinary use of "Xylocaine" spray, Taylor, P. M., (*C*) 113

Anaesthetic–analgesic regimens, Addition of droperidol to PCA morphine: what is the optimal dose? Lamond, C. T., *et al.*, (*ESA*) A.204

——, Blended anaesthesia in pediatric major surgery: top-up *vs* epidural continuous infusion, Savoia, G., *et al.*, (*ESA*) A.159

——, Diamorphine/bupivacaine mixture *vs* plain bupivacaine: a comparison of epidural infusions in labour, Bailey, C. R., *et al.*, (*ESA*) A.169

——, Fentanyl or buprenorphine side effects in spinal anaesthesia, Foppoli, R., *et al.*, (*ESA*) A.132

——, Patient-controlled extradural analgesia to compare bupivacaine, fentanyl and bupivacaine with fentanyl in the treatment of postoperative pain, Cooper, D. W., *et al.* 503–507

——, Postoperative hypoxaemia: comparison of epidural and patient controlled analgesia, Spencer, A., *et al.*, (*ESA*) A.207

——, Propofol anaesthesia with spontaneous breathing for extracorporeal shock wave lithotripsy, Pasch, T., *et al.*, (*ESA*) A.153

——, Propofol and alfentanil mixture, Sandin, R., (*C*) 382–383

——, Propofol and alfentanil mixture, Taylor, I. N., *et al.*, (*C*) 383

——, Subarachnoid anaesthesia (SAA) and postoperative analgesia with bupivacaine (BV) plus fentanyl (FN) in geriatric patients, Fernandez, D., *et al.*, (*ESA*) A.131

Anaesthetic techniques, bronchoscopy, Comparison of midazolam with propofol for sedation in outpatient bronchoscopy, Crawford, M., *et al.* 419–422

——, Fiberoptic bronchoscopy in brain dead organ donors, Riou, B., *et al.*, (*ESA*) A.80

Anaesthetic techniques, endobronchial, A bifurcated endobronchial tube in the management of laryngotracheo-oesophageal cleft repair, Ahmad, R., *et al.* 696–698

——, Continuous spirometry for detection of double-lumen endobronchial tube displacement, Bardoczky, G. I., *et al.* 499–502

——, Double-lumen tubes, Vaughan, R. S., (*E*) 497–498

——, Endobronchial cuff pressures, Cobley, M., *et al.* 576–578

——, Transthoracic endoscopic sympathectomy, Gilligan, S., *et al.*, (*C*) 491

——, Transthoracic endoscopic sympathectomy, Jedeiken, R., *et al.*, (*C*) 491–492

——, Transthoracic endoscopic sympathectomy, Plastow, S. E., *et al.*, (*C*) 492

Anaesthetic techniques, extradural, A continuous subdural block, Collier, C. B., *et al.* 462–465

——, Aspirin, bleeding time and central neural block, Wildsmith, J. A. W., *et al.*, (*C*) 112

——, Blended anaesthesia in pediatric major surgery: top-up *vs* epidural continuous infusion, Savoia, G., *et al.*, (*ESA*) A.159

——, Delayed presentation of an extradural abscess in a patient with alcohol abuse, Nordström, O., *et al.* 368–369

——, Direct spinal effect of intrathecal and extradural midazolam on visceral noxious stimulation in rabbits, Crawford, M. E., *et al.* 642–646

——, Does exogenous dopamine reverse cardiovascular depression induced by isoflurane during thoracic epidural blockade? Raner, C., *et al.*, (*ESA*) A.49

——, Effects of epidural clonidine on anaesthetic requirements and postoperative analgesia, Samsó, E., *et al.*, (*ESA*) A.205

——, Epidural blood patch for treatment of postdural puncture headache, Rosenberg, P. H., *et al.*, (*ESA*) A.129

——, Extradural abscess after central nerve block, Wildsmith, J. A. W., (*E*) 387–388

——, Extradural abscess in the postpartum period, Kitching, A. J., *et al.*, (*C*) 703

——, Extradural abscess in the postpartum period, Ngan Kee, W. D., (*C*) 704

——, Extradural abscess in the postpartum period, Vasdev, G. M. S., *et al.*, (*C*) 703–704

——, Face masks and spinal anaesthesia, O'Kelly, S. W., *et al.*, (*C*) 239

——, Face masks and spinal anaesthesia, Wildsmith, J. A. W., (*C*) 239

——, Influence of cervicothoracic epidural anaesthesia (C-TEA) on left ventricular (LV) contractility—an experimental study in pigs with autonomous blockade, Reiz, S., *et al.*, (*ESA*) A.52

——, Long-term backache after extradural or general anaesthesia for manual removal of placenta: preliminary report, Vickers, R. J., *et al.* 214–215

——, Lumbovertebral syndrome after extradural blood patch, Seeberger, M. D., *et al.*, (*C*) 489

——, Lumbovertebral syndrome after extradural blood patch, Stride, P. C., (*C*) 489

——, Metal particle generation caused by the combined spinal–extradural technique, Hargreaves, J., (*C*) 706

——, Patient-controlled extradural analgesia to compare bupivacaine, fentanyl and bupivacaine with fentanyl in the treatment of postoperative pain, Cooper, D. W., *et al.* 503–507

——, Prevention and treatment of hypotension during central neural block, McCrae, A. F., *et al.* 672–680

——, Sequential spinal peridural anaesthesia for gynaecological surgery under laparoscopy, Joos, S., *et al.*, (*ESA*) A.130

——, Subdural catheterization and cord damage, Collier, C. B., (*C*) 384

——, Subdural catheterization and cord damage, McMenemin, I., (*C*) 384

——, The effect of parenteral diclofenac and morphine on efficacy duration and height of blockade during continuous epidural bupivacaine 0.5%, Forbes, D., *et al.*, (*ESA*) A.125

——, The effects of epidural and spinal anesthesia on the changes in the plethysmographic signal in the lower and upper limbs, Preisman, S., *et al.*, (*ESA*) A.124

——, Visualization of extradural blood patch for post lumbar puncture headache by magnetic resonance imaging, Griffiths, A. G., *et al.* 223–225

Anaesthetic techniques, fibreoptic, Comparison of midazolam with propofol for sedation in outpatient bronchoscopy, Crawford, M., *et al.* 419–422

——, Direct, indirect or flexible laryngoscopy after thyroidectomy? Lacoste, L., *et al.*, (*ESA*) A.66

Anaesthetic techniques, hypotensive, Does nicardipine potentiate the neuromuscular block of atracurium? Bazin, J. E., *et al.*, (*ESA*) A.136

Anaesthetic techniques, hypothermia, Core–peripheral temperature difference in early *vs* later extubation after coronary artery surgery, Knapik, P., *et al.*, (*ESA*) A.69

Anaesthetic techniques, i.m., Slow-release effect of pH-adjusted bupivacaine: pharmacokinetic demonstration, Benhamou, D., *et al.*, (*ESA*) A.120

Anaesthetic techniques, induction, Comparison of infusion rates of three i.v. anaesthetic agents for induction in elderly patients, Berthoud, M. C., *et al.* 423–427

——, Determination of a pharmacokinetic model for propofol induction of anaesthesia, Viviand, X., *et al.*, (*ESA*) A.150

——, Effects of etomidate on the adrenocortical and metabolic adaptation of the neonate, Crozier, T. A., *et al.* 47–53

——, Plasma catecholamines and neonatal condition after induction of anaesthesia with propofol or thiopentone at Caesarean section, Gin, T., *et al.* 311–316

——, Propofol and alfentanil or thiopentone and suxamethonium for tracheal intubation, Beck, G. N., *et al.*, (*ARS*) 483P

——, Quality of induction: a clinical comparison of Etomidat-Lipuro® and Hypnomidate®, Wiebalck, A., *et al.*, (*ESA*) A.154

Anaesthetic techniques, inhalation, Alterations in pain threshold and psychomotor response associated with subanaesthetic concentrations of inhalation anaesthetics in humans, Tomi, K., *et al.* 684–686

——, Influence of anaesthesia on post-operative hypoxaemia, Georgiou, L., *et al.*, (*ESA*) A.60

——, Is correlation of arterial and end-tidal carbon dioxide pressure during inhalation anaesthesia better with laryngeal mask as compared to face mask? Ivens, D., *et al.*, (*ESA*) A.17

——, I.v. anaesthesia with propofol using a target-controlled infusion system: comparison with inhalation anaesthesia for general surgical procedures in children, Doyle, E., *et al.* 542–555

——, Nitrous oxide-mediated activation of the EEG during isoflurane anaesthesia in patients, Yli-Hankala, A., *et al.* 54–57

——, Ventilation with halothane is less affected in children with laryngeal mask airway than with endotracheal tube, Reignier, J., *et al.*, (*ESA*) A.162

Anaesthetic techniques, insufflation, Abdominal wall retraction may decrease anaesthesiological risks of laparoscopic cholecystectomy, Vereczkey, Z., *et al.*, (*ESA*) A.64

——, Haemodynamic changes in patients undergoing laparoscopic cholecystectomy: measurement by transthoracic electrical bioimpedance, Critchley, L. A. H., *et al.* 681–683

——, Influence of pneumoperitoneum and posture on hemodynamic and stress responses during anaesthesia for laparoscopic surgery, Odeberg, S., *et al.*, (*ESA*) A.34

——, Neuroendocrine changes during pneumoperitoneum for laparoscopic cholecystectomy, Joris, J., *et al.*, (*ESA*) A.33

——, Respiratory effects of laparoscopic cholecystectomy (preliminary data), Crea, M. A., *et al.*, (*ESA*) A.63

Anaesthetic techniques, i.v., Continuous monitoring of Sp_{O_2} during total intravenous anaesthesia with ketamine and spontaneous ventilation, Joly, L.-M., *et al.*, (*ESA*) A.58

——, Influence of anaesthesia on post-operative hypoxaemia, Georgiou, L., *et al.*, (*ESA*) A.60

——, Plasma concentrations of midazolam after i.v., nasal or rectal administration in children, Malinovsky, J.-M., *et al.* 617–620

——, Total intravenous anaesthesia (TIVA) with propofol and alfentanil for renal transplantation, Kirvelä, M., *et al.*, (*ESA*) A.81

——, Tracheal intubation after induction of anaesthesia with propofol, alfentanil and i.v. lignocaine, Davidson, J. A. H., *et al.* 163–166

Anaesthetic techniques, i.v. bolus, I.v. bolus administration of subconvulsive doses of lignocaine to conscious sheep: relationships between myocardial pharmacokinetics and pharmacodynamics, Huang, Y. F., *et al.* 556–561

——, Spontaneous excitatory movements during recovery from propofol anaesthesia in an infant: EEG evaluation, Borgeat, A., *et al.* 459–461

Anaesthetic techniques, i.v. infusion, Closed-loop feedback controlled administration of alfentanil during alfentanil–nitrous oxide anaesthesia, Schwilden, H., *et al.* 389–393

——, Comparison of infusion rates of three i.v. anaesthetic agents for induction in elderly patients, Berthoud, M. C., *et al.* 423–427

——, Comparison of midazolam with propofol for sedation in outpatient bronchoscopy, Crawford, M., *et al.* 419–422

——, Computer-controlled syringe pump improves safety of

pharmacokinetic models, Duranteau, R., *et al.*, (*ESA*) A.148
——, Determination of a pharmacokinetic model for propofol induction of anaesthesia, Viviand, X., *et al.*, (*ESA*) A.150
——, Different rates of injection of propofol, Goodman, N. W., (*C*) 383
——, Different rates of injection of propofol, Peacock, J. E., *et al.*, (*C*) 383–384
——, I.v. anaesthesia with propofol using a target-controlled infusion system: comparison with inhalation anaesthesia for general surgical procedures in children, Doyle, E., *et al.* 542–555
——, Midazolam–alfentanil: an anaesthetic? An investigation using the isolated forearm technique, Russell, I. F. 42–46
——, Pharmacokinetics of propofol administered by infusion in dogs undergoing surgery, Nolan, A., *et al.* 546–551
——, Pharmacokinetics of propofol and its conjugates after continuous infusion in normal and renal failure patients, Nathan, N., *et al.*, (*ESA*) A.151
——, Prolonged (> 1 week) sedation with midazolam in ICU patients: efficacy, safety and pharmacokinetics, Heytens, L., *et al.*, (*ESA*) A.178
——, Propofol anaesthesia with spontaneous breathing for extracorporeal shock wave lithotripsy, Pasch, T., *et al.*, (*ESA*) A.153
Anaesthetic techniques, i.v. regional, Comparison of the effect of EMLA cream, subcutaneous ring anaesthesia and a double cuff technique in the prevention of tourniquet pain, Tsai, Y.-C., *et al.* 394–396
——, Improvement in i.v. regional anaesthesia by re-exsanguination before surgery, Rawal, N., *et al.* 280–285
Anaesthetic techniques, laryngoscopy, Day 0 or day 3 laryngoscopy after thyroidectomy? Lacoste, L., *et al.*, (*ESA*) A.67
——, Direct, indirect or flexible laryngoscopy after thyroidectomy? Lacoste, L., *et al.*, (*ESA*) A.66
Anaesthetic techniques, neuroleptanaesthesia, Recoveries of post-tetanic twitch and train-of-four responses after administration of vecuronium with different inhalation anaesthetics and neuroleptanaesthesia, Saitoh, Y., *et al.* 402–404
Anaesthetic techniques, preoxygenation, Preoxygenation and Sp_{O_2} after induction of anaesthesia with propofol and fentanyl, Rittoo, D. B., *et al.*, (*ARS*) 486P
——, Routine preoxygenation: how long before mask anaesthesia? Head-Rapson, A. G., *et al.*, (*ARS*) 488P
Anaesthetic techniques, regional, I.v. anaesthesia with propofol using a target-controlled infusion system: comparison with inhalation anaesthesia for general surgical procedures in children, Doyle, E., *et al.* 542–555
——, Peripheral nerve damage and regional anaesthesia, Baranowski, A. P., *et al.*, (*C*) 593–594
——, Peripheral nerve damage and regional anaesthesia, Gentili, M. E., *et al.*, (*C*) 594
——, Peripheral nerve damage and regional anaesthesia, Rice, A. S. C., *et al.*, (*C*) 594
——, Sedation with propofol during regional anaesthesia, Arnold, B. D. C., (*C*) 112
Anaesthetic techniques, regional, brachial plexus, Clinical and radiological comparison of perivascular and transarterial techniques of axillary brachial plexus block, Pere, P., *et al.* 276–279
Anaesthetic techniques, regional, brachial plexus, Explaining risk to patients, Chambers, W. A., (*C*) 381–382
——, Explaining risk to patients, Potter, F. A., (*C*) 381
——, Motor blockade and absence of local nerve toxicity induced by liposomal bupivacaine injected into the axillary brachial plexus of rabbits, Legros, F. J., *et al.*, (*ESA*) A.122
Anaesthetic techniques, regional, caudal, Clonidine in paediatric caudal anaesthesia, Jamali, S., *et al.*, (*ESA*) A.160
Anaesthetic techniques, regional, intercostal, Efficacy of continuous intercostal bupivacaine for pain relief after thoracotomy, Dryden, C. M., *et al.* 508–510
Anaesthetic techniques, regional, intrapleural, Transthoracic endoscopic sympathectomy, Gilligan, S., *et al.*, (*C*) 491
——, Transthoracic endoscopic sympathectomy, Jedeiken, R., *et al.*, (*C*) 491–492
——, Transthoracic endoscopic sympathectomy, Plastow, S. E., *et al.*, (*C*) 492
Anaesthetic techniques, regional, knee, Pain relief after anterior cruciate ligament repair, Carroll, P. H., *et al.*, (*C*) 600
——, Pain relief after anterior cruciate ligament repair, Joshi, G. P., (*C*) 600
Anaesthetic techniques, regional, paravertebral, Plasma concentrations of bupivacaine and its enantiomers during continuous extrapleural intercostal nerve block, Berrisford, R. G., *et al.* 201–204
Anaesthetic techniques, subarachnoid, Best Quincke point needle for Caesarean section, Lyons, G., (*ESA*) A.174
——, Differential effects of alfentanil, fentanyl, pethidine and lignocaine administered intrathecally on nociceptive responses evoked by low and high frequency stimulation of somatic nerves, Wang, C., *et al.* 63–69
——, Direct spinal effect of intrathecal and extradural midazolam on visceral noxious stimulation in rabbits, Crawford, M. E., *et al.* 642–646
——, Effects of intrathecal meperidine (MP), fentanyl (FN) and lidocaine (LD) on somatosensory (SSEP) and cortical motor (CMEP) evoked potentials in humans, Fernandez, S., *et al.*, (*ESA*) A.119
——, Face masks and spinal anaesthesia, O'Kelly, S. W., *et al.*, (*C*) 239
——, Face masks and spinal anaesthesia, Wildsmith, J. A. W., (*C*) 239
——, Fentanyl or buprenorphine side effects in spinal anaesthesia, Foppoli, R., *et al.*, (*ESA*) A.132
——, Headache—new needles and spinal anaesthesia for C. section, Thormann, F., *et al.*, (*ESA*) A.173
——, Incidence of post dural puncture headache in young adults by the use of the Sprôtte needle: 300 patients, Descraques, C., *et al.*, (*ESA*) A.127
——, Incremental spinal anaesthesia for elective Caesarean section: maternal and fetal haemodynamic effects, Robson, S. C., *et al.* 634–638
——, Metal particle generation caused by the combined spinal–extradural technique, Hargreaves, J., (*C*) 706
——, Nine years of clinical experience with 29 gauge spinal needles, Dittmann, M., *et al.*, (*ESA*) A.126
——, Postdural puncture headaches are not related to the duration of spinal catheter placement, Liu, N., *et al.*, (*ESA*) A.128
——, Prevention and treatment of hypotension during central neural block, McCrae, A. F., *et al.* 672–680
——, Sequential spinal peridural anaesthesia for gynaecological surgery under laparoscopy, Joos, S., *et al.*, (*ESA*) A.130
——, Spinal anesthesia for C section: addition of phenylephrine to ephedrine for prevention of maternal hypotension, Thirion, A.-V., *et al.*, (*ESA*) A.172
——, Spread of spinal anaesthesia for Caesarean section in singleton and twin pregnancies, Jawan, B., *et al.* 639–641
——, Subarachnoid anaesthesia (SAA) and postoperative analgesia with bupivacaine (BV) plus fentanyl (FN) in geriatric patients, Fernandez, D., *et al.*, (*ESA*) A.131
——, The effects of epidural and spinal anesthesia on the changes in the plethysmographic signal in the lower and upper limbs, Preisman, S., *et al.*, (*ESA*) A.124
Anaesthetic techniques, subconvulsive dose, I.v. bolus administration of subconvulsive doses of lignocaine to conscious sheep: myocardial pharmacokinetics, Huang, Y. F., *et al.* 326–332
——, I.v. bolus administration of subconvulsive doses of lignocaine to conscious sheep: relationships between myocardial pharmacokinetics and pharmacodynamics, Huang, Y. F., *et al.* 556–561
Anaesthetic techniques, subcutaneous, Comparison of the effect of EMLA cream, subcutaneous ring anaesthesia and a double cuff technique in the prevention of tourniquet pain, Tsai, Y.-C., *et al.* 394–396
Anaesthetic techniques, subdural, A continuous subdural block, Collier, C. B., *et al.* 462–465
Anaesthetic techniques, test doses, Prediction of infusion rate of vecuronium to maintain steady state using the bolus test dose technique, Morgan, R. J., *et al.*, (*ARS*) 481P
Anaesthetic techniques, topical, Glycopyrronium prolongs topical anaesthesia of oral mucosa and enhances absorption of lignocaine, Watanabe, H., *et al.* 94–95
——, Laryngeal function as assessed by tussometry following topical anaesthesia, Mahajan, R. P., *et al.*, (*ESA*) A.68
Anaesthetics gases, nitrous oxide, Alterations in pain threshold and psychomotor response associated with subanaesthetic concentrations of inhalation anaesthetics in humans, Tomi, K., *et al.* 684–686
——, Brain partial pressures of isoflurane and nitrous oxide, Petersen-Felix, S., *et al.*, (*C*) 704–705
——, Brain partial pressures of isoflurane and nitrous oxide, Thornton, C., *et al.*, (*C*) 705
——, Effect of nitrous oxide on auditory evoked potentials, Jessop, J., *et al.*, (*C*) 380
——, Effect of nitrous oxide on auditory evoked potentials, Plourde, G., (*C*) 379–380
——, Effect of nitrous oxide on cerebral blood flow in normal humans, Field, L. M., *et al.* 154–159
——, Effects of nitrous oxide (N_2O) on systemic

haemodynamics, regional left ventricular (LV) function and incidence of myocardial ischaemia (MI) in vascular surgical patients with coronary artery disease (CAD), Hohner, P., *et al.*, (*ESA*) A.41
——, Influence of anaesthesia on post-operative hypoxaemia, Georgiou, L., *et al.*, (*ESA*) A.60
——, Neuromuscular blockade following mivacurium in children during N_2O–halothane, Orliaguet, G., *et al.*, (*ESA*) A.163
——, Nitrous oxide administration via oxygen therapy devices, Goddard, J. M., (*C*) 238
——, Nitrous oxide administration via oxygen therapy devices, Joshi, P., *et al.*, (*C*) 238
——, Nitrous oxide induced neuronal depression: modification through benzodiazepine receptors, Dzoljic, M., *et al.*, (*ESA*) A.112
——, Nitrous oxide-mediated activation of the EEG during isoflurane anaesthesia in patients, Yli-Hankala, A., *et al.* 54–57

Anaesthetics i.v., droperidol, Addition of droperidol to patient-controlled analgesia: effect on nausea and vomiting, Williams, O. A., *et al.*, (*ARS*) 479P
——, Addition of droperidol to PCA morphine: what is the optimal dose? Lamond, C. T., *et al.*, (*ESA*) A.204
——, Comparison of ondansetron, metoclopramide and droperidol for the prophylaxis of emetic symptoms after gynecological laparoscopic procedures, Geiger, C., *et al.*, (*ESA*) A.14
——, Double-blind comparison of ondansetron, droperidol and saline for prevention of nausea & vomiting after orthopaedic surgery, Gan, T. J., *et al.*, (*ESA*) A.13
——, Ondansetron 4 mg *vs* droperidol 1.25 mg in the prophylaxis of postoperative nausea and vomiting after alfentanil-supplemented inhalation anaesthesia, Alon, E., *et al.*, (*ESA*) A.12

Anaesthetics i.v., etomidate, Adrenocortical function: a clinical comparison of Etomidat-Lipuro® and Hypnomidate®, Wiebalck, A., *et al.*, (*ESA*) A.90
——, Changes in haemodynamic variables with thiopentone, methohexitone, propofol and etomidate, Price, M., (*C*) 116
——, Changes in haemodynamic variables with thiopentone, methohexitone, propofol and etomidate, Williams, E. L., (*C*) 115
——, Comparison of infusion rates of three i.v. anaesthetic agents for induction in elderly patients, Berthoud, M. C., *et al.* 423–427
——, Does etomidate cause haemolysis? Doenicke, A., *et al.*, (*C*) 491
——, Does etomidate cause haemolysis? Wertz, E., (*C*) 490–491
——, Effects of etomidate on the adrenocortical and metabolic adaptation of the neonate, Crozier, T. A., *et al.* 47–53
——, Quality of induction: a clinical comparison of Etomidat-Lipuro® and Hypnomidate®, Wiebalck, A., *et al.*, (*ESA*) A.154

Anaesthetics i.v., ketamine, Continuous monitoring of Sp_{O_2} during total intravenous anaesthesia with ketamine and spontaneous ventilation, Joly, L.-M., *et al.*, (*ESA*) A.58
——, Ketamine does not prevent hypotension caused by induction of anaesthesia with propofol in elderly patients, Blockmans, D., *et al.*, (*ESA*) A.40
——, Midazolam prevents ketamine-induced stimulation of cerebral metabolism, Åkeson, J., *et al.*, (*ESA*) A.111
——, Pharmacokinetics and pharmacodynamics of ketamine enantiomers in surgical patients using a stereoselective analytical method, Geisslinger, G., *et al.* 666–671

Anaesthetics i.v., methohexitone, Changes in haemodynamic variables with thiopentone, methohexitone, propofol and etomidate, Price, M., (*C*) 116
——, Changes in haemodynamic variables with thiopentone, methohexitone, propofol and etomidate, Williams, E. L., (*C*) 115
——, Comparison of infusion rates of three i.v. anaesthetic agents for induction in elderly patients, Berthoud, M. C., *et al.* 423–427
——, Effects of etomidate on the adrenocortical and metabolic adaptation of the neonate, Crozier, T. A., *et al.* 47–53

Anaesthetics i.v., propofol, Alizapride does reduce pain on injection of propofol: comparison with lidocaine, Zaouk, G., *et al.*, (*ESA*) A.11
——, An alternative method of increasing Pco_2 using apnoea and continuous positive airway pressure, Karlsten, R., *et al.* 411–413
——, Cardiovascular effects of i.v. induction in children: comparison between propofol and thiopentone, Aun, C. S. T., *et al.* 647–653
——, Changes in haemodynamic variables with thiopentone, methohexitone, propofol and etomidate, Price, M., (*C*) 116
——, Changes in haemodynamic variables with thiopentone, methohexitone, propofol and etomidate, Williams, E. L., (*C*) 115
——, Comparison of alfentanil with suxamethonium in facilitating nasotracheal intubation in day-case anaesthesia, Alcock, R., *et al.* 34–37
——, Comparison of midazolam with propofol for sedation in outpatient bronchoscopy, Crawford, M., *et al.* 419–422
——, Comparison of recovery from anaesthesia induced in children with either propofol or thiopentone, Runcie, C. J., *et al.* 192–195
——, Comparison of the sedative and amnesic effects of midazolam and propofol, Polster, M. R., *et al.* 612–616
——, Determination of a pharmacokinetic model for propofol induction of anaesthesia, Viviand, X., *et al.*, (*ESA*) A.150
——, Different rates of injection of propofol, Goodman, N. W., (*C*) 383
——, Different rates of injection of propofol, Peacock, J. E., *et al.*, (*C*) 383–384
——, Does propofol supplemented anaesthesia affect neurophysiological outcome following cardiopulmonary bypass? Phillips, A. S., *et al.*, (*ARS*) 484P
——, Effect of hyperoxia on the breathing of patients anaesthetized with infusions of propofol, Dow, A. C., *et al.* 532–535
——, Effect of propofol on neutrophil respiratory burst, Ogilvy, A. J., *et al.*, (*ARS*) 476P
——, Effects of active and passive sighs in normoxia and hyperoxia on the breathing of patients anaesthetized with infusions of propofol, Goodman, N. W., *et al.* 536–541
——, Gastric mucosal perfusion is better preserved during cardiac surgery when isoflurane rather than enflurane or propofol is used to maintain anaesthesia, Mythen, M., *et al.*, (*ESA*) A.29
——, Haemodynamic and catecholamine responses to induction of anaesthesia and tracheal intubation: comparison between propofol and thiopentone, Lindgren, L., *et al.* 306–310
——, Influence of anaesthesia on post-operative hypoxaemia, Georgiou, L., *et al.*, (*ESA*) A.60
——, I.v. anaesthesia with propofol using a target-controlled infusion system: comparison with inhalation anaesthesia for general surgical procedures in children, Doyle, E., *et al.* 542–555
——, Ketamine does not prevent hypotension caused by induction of anaesthesia with propofol in elderly patients, Blockmans, D., *et al.*, (*ESA*) A.40
——, Metabolic effects of propofol and flunitrazepam given for sedation after aortic surgery, Moritz, F., *et al.* 451–453
——, Pain on i.v. injection of metoclopramide, Wilkinson, D. J., (*C*) 239
——, Pharmacokinetics of propofol administered by infusion in dogs undergoing surgery, Nolan, A., *et al.* 546–551
——, Pharmacokinetics of propofol and its conjugates after continuous infusion in normal and renal failure patients, Nathan, N., *et al.*, (*ESA*) A.151
——, Plasma catecholamines and neonatal condition after induction of anaesthesia with propofol or thiopentone at Caesarean section, Gin, T., *et al.* 311–316
——, Preoxygenation and Sp_{O_2} after induction of anaesthesia with propofol and fentanyl, Rittoo, D. B., *et al.*, (*ARS*) 486P
——, Propofol (2,6 diisopropylphenol) as an antioxidant *in-vitro*: a dose response study, Bennett, S., *et al.*, (*ESA*) A.152
——, Propofol anaesthesia with spontaneous breathing for extracorporeal shock wave lithotripsy, Pasch, T., *et al.*, (*ESA*) A.153
——, Propofol and alfentanil mixture, Sandin, R., (*C*) 382–383
——, Propofol and alfentanil mixture, Taylor, I. N., *et al.*, (*C*) 383
——, Propofol and alfentanil or thiopentone and suxamethonium for tracheal intubation, Beck, G. N., *et al.*, (*ARS*) 483P
——, Propofol decreases random and chemotactic stimulated locomotion of human neutrophils *in vitro*, Jensen, A. G., *et al.* 99–100
——, Propofol for tracheal intubation in paediatric outpatient anaesthesia, Montasser, A. M., (*ESA*) A.161
——, Propofol/fentanyl-anesthesia in patients with highly depressed cardiac function, Rauch, H., *et al.*, (*ESA*) A.30
——, Sedation with propofol during regional anaesthesia, Arnold, B. D. C., (*C*) 112
——, Spontaneous excitatory movements during recovery from propofol anaesthesia in an infant: EEG evaluation, Borgeat, A., *et al.* 459–461

——, Target-controlled intravenous sedation with propofol, Mergaert, C., *et al.*, (*ESA*) A.149
——, Total intravenous anaesthesia (TIVA) with propofol and alfentanil for renal transplantation, Kirvelä, M., *et al.*, (*ESA*) A.81
——, Tracheal intubation after induction of anaesthesia with propofol, alfentanil and i.v. lignocaine, Davidson, J. A. H., *et al.* 163–166
——, Transcranial Doppler sonography: effect of propofol and thiopental in patients with brain tumors and brain injuries, Schregel, W., *et al.*, (*ESA*) A.105
——, Use of alfentanil with propofol for nasotracheal intubation without neuromuscular block, Coghlan, S. F. E., *et al.* 89–91
Anaesthetics i.v., stereoisomers, Pharmacokinetics and pharmacodynamics of ketamine enantiomers in surgical patients using a stereoselective analytical method, Geisslinger, G., *et al.* 666–671
Anaesthetics i.v., thiopentone, An alternative method of increasing $P\text{co}_2$ using apnoea and continuous positive airway pressure, Karlsten, R., *et al.* 411–413
——, Cardiovascular effects of i.v. induction in children: comparison between propofol and thiopentone, Aun, C. S. T., *et al.* 647–653
——, Changes in haemodynamic variables with thiopentone, methohexitone, propofol and etomidate, Price, M., (*C*) 116
——, Changes in haemodynamic variables with thiopentone, methohexitone, propofol and etomidate, Williams, E. L., (*C*) 115
——, Comparison of infusion rates of three i.v. anaesthetic agents for induction in elderly patients, Berthoud, M. C., *et al.* 423–427
——, Comparison of recovery from anaesthesia induced in children with either propofol or thiopentone, Runcie, C. J., *et al.* 192–195
——, Haemodynamic and catecholamine responses to induction of anaesthesia and tracheal intubation: comparison between propofol and thiopentone, Lindgren, L., *et al.* 306–310
——, Plasma catecholamines and neonatal condition after induction of anaesthesia with propofol or thiopentone at Caesarean section, Gin, T., *et al.* 311–316
——, Postoperative pain thresholds, Cook, T. M., (*C*) 110
——, Propofol and alfentanil or thiopentone and suxamethonium for tracheal intubation, Beck, G. N., *et al.*, (*ARS*) 483P
——, Transcranial Doppler sonography: effect of propofol and thiopental in patients with brain tumors and brain injuries, Schregel, W., *et al.*, (*ESA*) A.105
Anaesthetics local, bupivacaine, A continuous subdural block, Collier, C. B., *et al.* 462–465
——, Analgesia by wound infiltration before or after surgery in inguinal hernioraphy, Hennart, D., *et al.*, (*ESA*) A.202
——, Blended anaesthesia in pediatric major surgery: top-up *vs* epidural continuous infusion, Savoia, G., *et al.*, (*ESA*) A.159
——, Clinical and radiological comparison of perivascular and transarterial techniques of axillary brachial plexus block, Pere, P., *et al.* 276–279
——, Continuous subarachnoid infusion of 0.125% bupivacaine for analgesia during labour, McHale, S., *et al.*, (*C*) 701
——, Continuous subarachnoid infusion of 0.125% bupivacaine for analgesia during labour, Russell, R., (*C*) 699–700
——, Delayed presentation of an extradural abscess in a patient with alcohol abuse, Nordström, O., *et al.* 368–369
——, Diamorphine/bupivacaine mixture *vs* plain bupivacaine: a comparison of epidural infusions in labour, Bailey, C. R., *et al.*, (*ESA*) A.169
——, Diaphragmatic function after bupivacaine cervical extradural analgesia for chronic pain therapy, Nyström, E., *et al.*, (*ESA*) A.65
——, Effect of extradural analgesia on stress responses to abdominal surgery in infants, Wolf, A. R., *et al.* 654–660
——, Efficacy of continuous intercostal bupivacaine for pain relief after thoracotomy, Dryden, C. M., *et al.* 508–510
——, Epidural administration of liposomal bupivacaine for the management of postsurgical pain, Boogaerts, J., *et al.*, (*ESA*) A.200
——, Extradural 0.07% bupivacaine for postoperative pain, Slade, J. M., (*ARS*) 478P
——, Fentanyl or buprenorphine side effects in spinal anaesthesia, Foppoli, R., *et al.*, (*ESA*) A.132
——, *In vivo* determination of concentration–effect curves of local anaesthetics in man, Wiesemes, R., *et al.* 552–555
——, Intermittent *vs* continuous extradural infusion of bupivacaine during labour, Eddleston, J. M., (*C*) 490
——, Intermittent *vs* continuous extradural infusion of bupivacaine during labour, Laishley, R. S., (*C*) 490
——, Lemakalim reverses ventricular conduction impairment induced by a large dose of bupivacaine in anesthetized dogs, de La Coussaye, J. E., *et al.*, (*ESA*) A.121
——, Motor blockade and absence of local nerve toxicity induced by liposomal bupivacaine injected into the axillary brachial plexus of rabbits, Legros, F. J., *et al.*, (*ESA*) A.122
——, Pain relief for infants undergoing abdominal surgery: comparison of infusions of i.v. morphine and extradural bupivacaine, Wolf, A. R., *et al.* 10–16
——, Patient controlled epidural analgesia *vs* intermittent injections during labor using 0.125% bupivacaine and sufentanil, Baudot, J., *et al.*, (*ESA*) A.170
——, Patient-controlled extradural analgesia to compare bupivacaine, fentanyl and bupivacaine with fentanyl in the treatment of postoperative pain, Cooper, D. W., *et al.* 503–507
——, Plasma concentrations of bupivacaine and its enantiomers during continuous extrapleural intercostal nerve block, Berrisford, R. G., *et al.* 201–204
——, Postoperative hypoxaemia: comparison of epidural and patient controlled analgesia, Spencer, A., *et al.*, (*ESA*) A.207
——, Pre-emptive analgesia, Dahl, J. B., *et al.*, (*C*) 379
——, Pre-emptive analgesia, Katz, J., *et al.*, (*C*) 378
——, Slow-release effect of pH-adjusted bupivacaine: pharmacokinetic demonstration, Benhamou, D., *et al.*, (*ESA*) A.120
——, Spread of spinal anaesthesia for Caesarean section in singleton and twin pregnancies, Jawan, B., *et al.* 639–641
——, Subarachnoid anaesthesia (SAA) and postoperative analgesia with bupivacaine (BV) plus fentanyl (FN) in geriatric patients, Fernandez, D., *et al.*, (*ESA*) A.131
——, The effect of parenteral diclofenac and morphine on efficacy duration and height of blockade during continuous epidural bupivacaine 0.5%, Forbes, D., *et al.*, (*ESA*) A.125
——, The effects of bupivacaine, mepivacaine and prilocaine on platelet aggregation, Bayhan, N., *et al.*, (*ESA*) A.123
——, Use of thoracic epidural block for perioperative analgesia in children, Entress, A. H., *et al.*, (*ESA*) A.158
Anaesthetics local, EMLA, Comparison of the effect of EMLA cream, subcutaneous ring anaesthesia and a double cuff technique in the prevention of tourniquet pain, Tsai, Y.-C., *et al.* 394–396
Anaesthetics local, lignocaine, Adrenaline-induced hypotension in neurosurgery, Phillips, S., *et al.* 687–688
——, Alizapride does reduce pain on injection of propofol: comparison with lidocaine, Zaouk, G., *et al.*, (*ESA*) A.11
——, Comparison of the effect of EMLA cream, subcutaneous ring anaesthesia and a double cuff technique in the prevention of tourniquet pain, Tsai, Y.-C., *et al.* 394–396
——, Differential effects of alfentanil, fentanyl, pethidine and lignocaine administered intrathecally on nociceptive responses evoked by low and high frequency stimulation of somatic nerves, Wang, C., *et al.* 63–69
——, Effect of esmolol *versus* lidocaine on intracranial pressure and haemodynamic responses to laryngoscopy and intubation, Samaha, T., *et al.*, (*ESA*) A.118
——, Effects of intradermal lignocaine and mepivacaine on human cutaneous circulation in areas with histamine-induced neurogenic inflammation, Fruhstorfer, H., *et al.* 167–172
——, Effects of intrathecal meperidine (MP), fentanyl (FN) and lidocaine (LD) on somatosensory (SSEP) and cortical motor (CMEP) evoked potentials in humans, Fernandez, S., *et al.*, (*ESA*) A.119
——, Fentanyl, as pethidine, inhibits post anaesthesia shivering, Alfonsi, P., *et al.*, (*ESA*) A.74
——, Glycopyrronium prolongs topical anaesthesia of oral mucosa and enhances absorption of lignocaine, Watanabe, H., *et al.* 94–95
——, Improvement in i.v. regional anaesthesia by re-exsanguination before surgery, Rawal, N., *et al.* 280–285
——, I.v. bolus administration of subconvulsive doses of lignocaine to conscious sheep: myocardial pharmacokinetics, Huang, Y. F., *et al.* 326–332
——, I.v. bolus administration of subconvulsive doses of lignocaine to conscious sheep: relationships between myocardial pharmacokinetics and pharmacodynamics, Huang, Y. F., *et al.* 556–561
——, Laryngeal function as assessed by tussometry following topical anaesthesia, Mahajan, R. P., *et al.*, (*ESA*) A.68
——, Pain on i.v. injection of metoclopramide, Wilkinson, D. J., (*C*) 239
——, The pressor response to venous cannulation: attenuation

by prior infiltration with local anaesthetic, Langham, B. T., *et al.* 519–521
——, Tracheal intubation after induction of anaesthesia with propofol, alfentanil and i.v. lignocaine, Davidson, J. A. H., *et al.* 163–166
——, Use of lignocaine in ventricular defibrillation? Baskett, P. J. F., (*C*) 380
——, Use of lignocaine in ventricular defibrillation? Quiney, N. F., *et al.*, (*C*) 380
Anaesthetics local, mepivacaine, Clinical and radiological comparison of perivascular and transarterial techniques of axillary brachial plexus block, Pere, P., *et al.* 276–279
——, Effects of intradermal lignocaine and mepivacaine on human cutaneous circulation in areas with histamine-induced neurogenic inflammation, Fruhstorfer, H., *et al.* 167–172
——, Improvement in i.v. regional anaesthesia by re-exsanguination before surgery, Rawal, N., *et al.* 280–285
——, The effects of bupivacaine, mepivacaine and prilocaine on platelet aggregation, Bayhan, N., *et al.*, (*ESA*) A.123
Anaesthetics local, prilocaine, Improvement in i.v. regional anaesthesia by re-exsanguination before surgery, Rawal, N., *et al.* 280–285
——, The effects of bupivacaine, mepivacaine and prilocaine on platelet aggregation, Bayhan, N., *et al.*, (*ESA*) A.123
Anaesthetics local, stereoisomers, Plasma concentrations of bupivacaine and its enantiomers during continuous extrapleural intercostal nerve block, Berrisford, R. G., *et al.* 201–204
Anaesthetics local, Xylocaine, Veterinary use of "Xylocaine" spray, Taylor, P. M., (*C*) 113
Anaesthetics volatile, desflurane, Hepatic elimination of diazepam: interactions with albumin, desflurane and sevoflurane, Dale, O., *et al.* 454–455
——, Hepatotoxicity of volatile anaesthetics, Elliott, R. H., *et al.* 339–348
——, Local *versus* neurogenic vasodilator effects of desflurane and isoflurane in the small intestine, Sundeman, H., *et al.*, (*ESA*) A.50
Anaesthetics volatile, diethyl ether, John Henry Hill Lewellin: The first etherist in Glasgow, Macdonald, A. G. 228–234
Anaesthetics volatile, enflurane, Alterations in pain threshold and psychomotor response associated with subanaesthetic concentrations of inhalation anaesthetics in humans, Tomi, K., *et al.* 684–686
——, An alternative method of increasing P_{CO_2} using apnoea and continuous positive airway pressure, Karlsten, R., *et al.* 411–413
——, Clonal variation in response to enflurane anaesthesia with *Daphnia magna*, Myles, A. P., *et al.*, (*ARS*) 476–477P
——, Effects of oral preoperative guanfacine on anesthetics requirements, Engelman, E., *et al.*, (*ESA*) A.144
——, Gastric mucosal perfusion is better preserved during cardiac surgery when isoflurane rather than enflurane or propofol is used to maintain anaesthesia, Mythen, M., *et al.*, (*ESA*) A.29
——, Hepatotoxicity of volatile anaesthetics, Elliott, R. H., *et al.* 339–348
——, Recoveries of post-tetanic twitch and train-of-four responses after administration of vecuronium with different inhalation anaesthetics and neuroleptanaesthesia, Saitoh, Y., *et al.* 402–404
——, Test-tube equilibration of volatile anaesthetic concentrations, Martin, D. C., *et al.* 365–367
Anaesthetics volatile, ether, Preoperative drinking and gastric contents, Levy, D. M., *et al.*, (*C*) 701–702
Anaesthetics volatile, halothane, Alterations in pain threshold and psychomotor response associated with subanaesthetic concentrations of inhalation anaesthetics in humans, Tomi, K., *et al.* 684–686
——, Comparison of *in vitro* contracture testing with ryanodine, halothane and caffeine in malignant hyperthermia and other neuromuscular disorders, Hopkins, P. M., *et al.* 397–401
——, Effect of age, gender and anaesthetic technique on the pharmacodynamics of atracurium, Parker, C. J. R., *et al.* 38–41
——, Haemodynamic changes produced by inhalation anaesthetics in the presence of phosphodiesterase inhibition, Molter, G., *et al.* 428–433
——, Halothane enhances forskolin stimulated cyclic adenosine-3′,5′-monophosphate formation in human neuroblastoma cells, Hirst, R. A., *et al.*, (*ARS*) 486P
——, Halothane, metabolite-induced antibodies and hepatotoxicity, Kenna, J. G., *et al.*, (*ARS*) 484–485P
——, Hepatotoxicity of volatile anaesthetics, Elliott, R. H., *et al.* 339–348
——, *In vitro* effect of ephedrine, adrenaline, noradrenaline and isoprenaline on halothane-induced contractures in skeletal muscle from patients potentially susceptible to malignant hyperthermia, Urwyler, A., *et al.* 76–79
——, Isoproterenol reverses the MAC decreasing effect of esmolol in rats, Perel, A., *et al.*, (*ESA*) A.117
——, I.v. anaesthesia with propofol using a target-controlled infusion system: comparison with inhalation anaesthesia for general surgical procedures in children, Doyle, E., *et al.* 542–555
——, Membrane action of volatile anaesthetics: effect of halothane on microviscosity, Appadu, B., *et al.*, (*ARS*) 477P
——, Neuromuscular blockade following mivacurium in children during N_2O–halothane, Orliaguet, G., *et al.*, (*ESA*) A.163
——, Recoveries of post-tetanic twitch and train-of-four responses after administration of vecuronium with different inhalation anaesthetics and neuroleptanaesthesia, Saitoh, Y., *et al.* 402–404
——, Regurgitation and the laryngeal mask airway, Brimacombe, J., *et al.*, (*C*) 381
——, Regurgitation and the laryngeal mask airway, Vanner, R. G., (*C*) 380–381
——, Test-tube equilibration of volatile anaesthetic concentrations, Martin, D. C., *et al.* 365–367
——, Ventilation with halothane is less affected in children with laryngeal mask airway than with endotracheal tube, Reignier, J., *et al.*, (*ESA*) A.162
Anaesthetics volatile, isoflurane, Accumulation of acetone in blood during long-term anaesthesia with closed systems, Strauß, J. M., *et al.* 363–364
——, Alterations in pain threshold and psychomotor response associated with subanaesthetic concentrations of inhalation anaesthetics in humans, Tomi, K., *et al.* 684–686
——, Anaesthetic properties of dimethylthiourea, Koblin, D. D., *et al.* 456–458
——, Brain partial pressures of isoflurane and nitrous oxide, Petersen-Felix, S., *et al.*, (*C*) 704–705
——, Brain partial pressures of isoflurane and nitrous oxide, Thornton, C., *et al.*, (*C*) 705
——, Components of the inspiratory–arterial isoflurane partial pressure difference, Landon, A. J., *et al.* 605–611
——, Does exogenous dopamine reverse cardiovascular depression induced by isoflurane during thoracic epidural blockade? Raner, C., *et al.*, (*ESA*) A.49
——, Does propofol supplemented anaesthesia affect neurophysiological outcome following cardiopulmonary bypass? Phillips, A. S., *et al.*, (*ARS*) 484P
——, Effect of age, gender and anaesthetic technique on the pharmacodynamics of atracurium, Parker, C. J. R., *et al.* 38–41
——, Effects of oral preoperative guanfacine on anesthetics requirements, Engelman, E., *et al.*, (*ESA*) A.144
——, Gastric mucosal perfusion is better preserved during cardiac surgery when isoflurane rather than enflurane or propofol is used to maintain anaesthesia, Mythen, M., *et al.*, (*ESA*) A.29
——, Haemodynamic changes produced by inhalation anaesthetics in the presence of phosphodiesterase inhibition, Molter, G., *et al.* 428–433
——, Hepatotoxicity of volatile anaesthetics, Elliott, R. H., *et al.* 339–348
——, Influence of anaesthesia on post-operative hypoxaemia, Georgiou, L., *et al.*, (*ESA*) A.60
——, Isoflurane inhibits Ca^{2+}-induced insulin secretion from electrically permeabilised islets of Langerhans, Desborough, J. P., *et al.*, (*ESA*) A.91
——, Local *versus* neurogenic vasodilator effects of desflurane and isoflurane in the small intestine, Sundeman, H., *et al.*, (*ESA*) A.50
——, Nitrous oxide-mediated activation of the EEG during isoflurane anaesthesia in patients, Yli-Hankala, A., *et al.* 54–57
——, Prolonged use of isoflurane in a patient with tetanus, Stevens, J. J. W. M., *et al.* 107–109
——, Recoveries of post-tetanic twitch and train-of-four responses after administration of vecuronium with different inhalation anaesthetics and neuroleptanaesthesia, Saitoh, Y., *et al.* 402–404
——, Validation of coherent frequency of the EEG as a measure of consciousness during anaesthesia, Munglani, R., *et al.*, (*ARS*) 483–484P
Anaesthetics volatile, methoxyflurane, Alterations in pain threshold and psychomotor response associated with subanaesthetic concentrations of inhalation anaesthetics in humans, Tomi, K., *et al.* 684–686
Anaesthetics volatile, sevoflurane, Alterations in pain threshold and psychomotor response associated with

subanaesthetic concentrations of inhalation anaesthetics in humans, Tomi, K., *et al.* 684–686
——, Hepatic elimination of diazepam: interactions with albumin, desflurane and sevoflurane, Dale, O., *et al.* 454–455
——, Hepatotoxicity of volatile anaesthetics, Elliott, R. H., *et al.* 339–348
——, Minimum alveolar concentration of sevoflurane in elderly patients, Nakajima, R., *et al.* 273–275
——, Recoveries of post-tetanic twitch and train-of-four responses after administration of vecuronium with different inhalation anaesthetics and neuroleptanaesthesia, Saitoh, Y., *et al.* 402–404
Anaesthetist, activity, Face masks and spinal anaesthesia, O'Kelly, S. W., *et al.*, (*C*) 239
——, Face masks and spinal anaesthesia, Wildsmith, J. A. W., (*C*) 239
——, Perioperative blood loss, Appadu, B., (*C*) 492–493
Analeptics, caffeine, Comparison of *in vitro* contracture testing with ryanodine, halothane and caffeine in malignant hyperthermia and other neuromuscular disorders, Hopkins, P. M., *et al.* 397–401
Analgesia, obstetric, Adequate pain relief with epidural analgesia during labor: why are women still dissatisified? Hamza, J., *et al.*, (*ESA*) A.171
——, Diamorphine/bupivacaine mixture *vs* plain bupivacaine: a comparison of epidural infusions in labour, Bailey, C. R., *et al.*, (*ESA*) A.169
——, Patient controlled epidural analgesia *vs* intermittent injections during labor using 0.125% bupivacaine and sufentanil, Baudot, J., *et al.*, (*ESA*) A.170
Analgesia, paediatric, Clonidine in paediatric caudal anaesthesia, Jamali, S., *et al.*, (*ESA*) A.160
——, Effect of extradural analgesia on stress responses to abdominal surgery in infants, Wolf, A. R., *et al.* 654–660
——, Pain relief for infants undergoing abdominal surgery: comparison of infusions of i.v. morphine and extradural bupivacaine, Wolf, A. R., *et al.* 10–16
——, Postoperative analgesia in children, Fell, D., (*E*) 4–5
——, Use of thoracic epidural block for perioperative analgesia in children, Entress, A. H., *et al.*, (*ESA*) A.158
Analgesia, patient-controlled, Addition of droperidol to patient-controlled analgesia: effect on nausea and vomiting, Williams, O. A., *et al.*, (*ARS*) 479P
——, Addition of droperidol to PCA morphine: what is the optimal dose? Lamond, C. T., *et al.*, (*ESA*) A.204
——, Evaluation of the analgesic effect of metoclopramide after opioid-free analgesia, Lisander, B. 631–633
——, Intrathecal pain relief in terminally ill cancer patients at home, Wagemans, M. F. M., *et al.*, (*ESA*) A.213
——, Patient-controlled analgesia by proxy, Lam, F. Y., (*C*) 113
——, Patient controlled epidural analgesia *vs* intermittent injections during labor using 0.125% bupivacaine and sufentanil, Baudot, J., *et al.*, (*ESA*) A.170
——, Patient-controlled extradural analgesia to compare bupivacaine, fentanyl and bupivacaine with fentanyl in the treatment of postoperative pain, Cooper, D. W., *et al.* 503–507
——, Postoperative hypoxaemia: comparison of epidural and patient controlled analgesia, Spencer, A., *et al.*, (*ESA*) A.207
——, Safety of PCA in elderly, Santangelo, E., *et al.*, (*ESA*) A.206
Analgesia, postoperative, Addition of droperidol to PCA morphine: what is the optimal dose? Lamond, C. T., *et al.*, (*ESA*) A.204
——, Clonidine in paediatric caudal anaesthesia, Jamali, S., *et al.*, (*ESA*) A.160
——, Diclofenac and ketoprofen for pain treatment after elective Caesarean section, Rorarius, M. G. F., *et al.* 293–297
——, Effect of morphine on a nociceptive flexion reflex in patients with postoperative pain, Chauvin, M., *et al.*, (*ESA*) A.115
——, Effects of epidural clonidine on anaesthetic requirements and postoperative analgesia, Samsó, E., *et al.*, (*ESA*) A.205
——, Efficacy of continuous intercostal bupivacaine for pain relief after thoracotomy, Dryden, C. M., *et al.* 508–510
——, Efficacy of postoperative pain treatment regimens using both buprenorphine and papaveretum sequentially after abdominal hysterectomy, Green, D. W., *et al.* 626–630
——, Epidural administration of liposomal bupivacaine for the management of postsurgical pain, Boogaerts, J., *et al.*, (*ESA*) A.200
——, Evaluation of pain and analgesia in a postanesthesia care unit, Aubrun, F., *et al.*, (*ESA*) A.198
——, Evaluation of the analgesic effect of metoclopramide after opioid-free analgesia, Lisander, B. 631–633
——, Extradural 0.07% bupivacaine for postoperative pain, Slade, J. M., (*ARS*) 478P
——, Intra-articular morphine for pain relief after anterior cruciate ligament repair, Joshi, G. P., *et al.* 87–88
——, Intranasal fentanyl for postoperative pain management in an unselected population, Striebel, W. H., *et al.*, (*ESA*) A.209
——, Ketorolac postoperative analgesia, Al-Hasani, A., (*C*) 112–113
——, Ketorolac postoperative analgesia, Kinsella, J., (*C*) 113
——, Organization of acute pain services—a low-cost model, Rawal, N., (*ESA*) A.199
——, Pain relief after anterior cruciate ligament repair, Carroll, P. H., *et al.*, (*C*) 600
——, Pain relief after anterior cruciate ligament repair, Joshi, G. P., (*C*) 600
——, Pain relief for infants undergoing abdominal surgery: comparison of infusions of i.v. morphine and extradural bupivacaine, Wolf, A. R., *et al.* 10–16
——, Partial reversal of the effects of extradural clonidine by oral yohimbine in postoperative patients, Liu, N., *et al.* 515–518
——, Patient-controlled extradural analgesia to compare bupivacaine, fentanyl and bupivacaine with fentanyl in the treatment of postoperative pain, Cooper, D. W., *et al.* 503–507
——, Postoperative analgesia: a two dosage regimens trial for i.m. morphine after early i.v. titration, Butscher, K., *et al.*, (*ESA*) A.201
——, Postoperative analgesia in children, Fell, D., (*E*) 4–5
——, Pre-emptive analgesia, Dahl, J. B., *et al.*, (*C*) 379
——, Pre-emptive analgesia, Katz, J., *et al.*, (*C*) 378
——, Preoperative indomethacin for pain relief after thoracotomy: comparison with postoperative indomethacin, Murphy, D. F., *et al.* 298–300
——, Subarachnoid anaesthesia (SAA) and postoperative analgesia with bupivacaine (BV) plus fentanyl (FN) in geriatric patients, Fernandez, D., *et al.*, (*ESA*) A.131
——, The effect of parenteral diclofenac and morphine on efficacy duration and height of blockade during continuous epidural bupivacaine 0.5%, Forbes, D., *et al.*, (*ESA*) A.125
——, The value of pre-emptive analgesia in the treatment of postoperative pain, Dahl, J. B., *et al.* 434–439
——, Ventilatory effects of morphine, pethidine and methadone in children, Hamunen, K. 414–418
Analgesia, pre-emptive, Analgesia by wound infiltration before or after surgery in inguinal hernioraphy, Hennart, D., *et al.*, (*ESA*) A.202
——, Pain relief after anterior cruciate ligament repair, Carroll, P. H., *et al.*, (*C*) 600
——, Pain relief after anterior cruciate ligament repair, Joshi, G. P., (*C*) 600
——, Pre-emptive analgesia, Dahl, J. B., *et al.*, (*C*) 379
——, Pre-emptive analgesia, Katz, J., *et al.*, (*C*) 378
——, Preemptive analgesia with epidural morphine, Nègre, I., *et al.*, (*ESA*) A.203
——, Pre-emptive extradural analgesia, Hardy, P. A. J., (*C*) 493
——, Preoperative indomethacin for pain relief after thoracotomy: comparison with postoperative indomethacin, Murphy, D. F., *et al.* 298–300
——, The value of pre-emptive analgesia in the treatment of postoperative pain, Dahl, J. B., *et al.* 434–439
Analgesic techniques, extradural, Adequate pain relief with epidural analgesia during labor: why are women still dissatisified? Hamza, J., *et al.*, (*ESA*) A.171
——, Diamorphine/bupivacaine mixture *vs* plain bupivacaine: a comparison of epidural infusions in labour, Bailey, C. R., *et al.*, (*ESA*) A.169
——, Diaphragmatic function after bupivacaine cervical extradural analgesia for chronic pain therapy, Nyström, E., *et al.*, (*ESA*) A.65
——, Effect of extradural analgesia on stress responses to abdominal surgery in infants, Wolf, A. R., *et al.* 654–660
——, Epidural administration of liposomal bupivacaine for the management of postsurgical pain, Boogaerts, J., *et al.*, (*ESA*) A.200
——, Epidural clonidine analgesia after major gynaecological surgery, Smilov, I., *et al.*, (*ESA*) A.176
——, Epidural clonidine and myocardial ischaemia after abdominal aortic surgery, Fulgencio, J. P., *et al.*, (*ESA*) A.42
——, Extradural 0.07% bupivacaine for postoperative pain, Slade, J. M., (*ARS*) 478P

——, Intermittent *vs* continuous extradural infusion of bupivacaine during labour, Eddleston, J. M., (*C*) 490

——, Intermittent *vs* continuous extradural infusion of bupivacaine during labour, Laishley, R. S., (*C*) 490

——, Pain relief for infants undergoing abdominal surgery: comparison of infusions of i.v. morphine and extradural bupivacaine, Wolf, A. R., *et al.* 10–16

——, Partial reversal of the effects of extradural clonidine by oral yohimbine in postoperative patients, Liu, N., *et al.* 515–518

——, Patient controlled epidural analgesia *vs* intermittent injections during labor using 0.125% bupivacaine and sufentanil, Baudot, J., *et al.*, (*ESA*) A.170

——, Patient-controlled extradural analgesia to compare bupivacaine, fentanyl and bupivacaine with fentanyl in the treatment of postoperative pain, Cooper, D. W., *et al.* 503–507

——, Postoperative hypoxaemia: comparison of epidural and patient controlled analgesia, Spencer, A., *et al.*, (*ESA*) A.207

——, Preemptive analgesia with epidural morphine, Nègre, I., *et al.*, (*ESA*) A.203

——, Pre-emptive extradural analgesia, Hardy, P. A. J., (*C*) 493

——, Spinal extradural abscess: pursuit of vigilance, Bromage, P. R. 471–473

——, Use of thoracic epidural block for perioperative analgesia in children, Entress, A. H., *et al.*, (*ESA*) A.158

Analgesic techniques, i.m., Pharmacokinetics and effects of i.m. alfentanil as premedication for outpatient cataract surgery, Ali-Melkkilä, T., *et al.*, (*ESA*) A.145

Analgesic techniques, infiltration, Analgesia by wound infiltration before or after surgery in inguinal herniorraphy, Hennart, D., *et al.*, (*ESA*) A.202

Analgesic techniques, infusion, Continuous subarachnoid infusion of 0.125% bupivacaine for analgesia during labour, McHale, S., *et al.*, (*C*) 701

——, Continuous subarachnoid infusion of 0.125% bupivacaine for analgesia during labour, Russell, R., (*C*) 699–700

——, Intrathecal pain relief in terminally ill cancer patients at home, Wagemans, M. F. M., *et al.*, (*ESA*) A.213

Analgesic techniques, intra-articular, Intra-articular morphine for pain relief after anterior cruciate ligament repair, Joshi, G. P., *et al.* 87–88

——, Pain relief after anterior cruciate ligament repair, Carroll, P. H., *et al.*, (*C*) 600

——, Pain relief after anterior cruciate ligament repair, Joshi, G. P., (*C*) 600

Analgesic techniques, i.v., Pain relief for infants undergoing abdominal surgery: comparison of infusions of i.v. morphine and extradural bupivacaine, Wolf, A. R., *et al.* 10–16

Analgesic techniques, nasal, Intranasal fentanyl for breakthrough cancer pain or incident pain, Striebel, W. H., *et al.*, (*ESA*) A.210

——, Intranasal fentanyl for postoperative pain management in an unselected population, Striebel, W. H., *et al.*, (*ESA*) A.209

——, Pharmacokinetics of intranasal fentanyl, Striebel, H. W., *et al.*, (*ESA*) A.208

Analgesic techniques, subarachnoid, Continuous subarachnoid infusion of 0.125% bupivacaine for analgesia during labour, McHale, S., *et al.*, (*C*) 701

——, Continuous subarachnoid infusion of 0.125% bupivacaine for analgesia during labour, Russell, R., (*C*) 699–700

——, Intrathecal pain relief in terminally ill cancer patients at home, Wagemans, M. F. M., *et al.*, (*ESA*) A.213

——, Involvement of μ, δ, and κ receptors in the inhibition by intrathecal morphine of a C-fibre evoked reflex in the rat, Guirimand, F., *et al.*, (*ESA*) A.116

Analgesics anti-inflammatory, steroid, Spinal extradural abscess: pursuit of vigilance, Bromage, P. R. 471–473

Analgesics non-opioid, diclofenac, Diclofenac and ketoprofen for pain treatment after elective Caesarean section, Rorarius, M. G. F., *et al.* 293–297

——, The effect of parenteral diclofenac and morphine on efficacy duration and height of blockade during continuous epidural bupivacaine 0.5%, Forbes, D., *et al.*, (*ESA*) A.125

Analgesics non-opioid, indomethacin, Preoperative indomethacin for pain relief after thoracotomy: comparison with postoperative indomethacin, Murphy, D. F., *et al.* 298–300

Analgesics non-opioid, ketoprofen, Diclofenac and ketoprofen for pain treatment after elective Caesarean section, Rorarius, M. G. F., *et al.* 293–297

Analgesics non-opioid, ketorolac, Ketorolac postoperative analgesia, Al-Hasani, A., (*C*) 112–113

——, Ketorolac postoperative analgesia, Kinsella, J., (*C*) 113

——, Safety of PCA in elderly, Santangelo, E., *et al.*, (*ESA*) A.206

Analgesics opioid, alfentanil, Closed-loop feedback controlled administration of alfentanil during alfentanil–nitrous oxide anaesthesia, Schwilden, H., *et al.* 389–393

——, Comparison of alfentanil with suxamethonium in facilitating nasotracheal intubation in day-case anaesthesia, Alcock, R., *et al.* 34–37

——, Differential effects of alfentanil, fentanyl, pethidine and lignocaine administered intrathecally on nociceptive responses evoked by low and high frequency stimulation of somatic nerves, Wang, C., *et al.* 63–69

——, Effects of oral preoperative guanfacine on anesthetics requirements, Engelman, E., *et al.*, (*ESA*) A.144

——, Midazolam–alfentanil: an anaesthetic? An investigation using the isolated forearm technique, Russell, I. F. 42–46

——, Ondansetron 4 mg *vs* droperidol 1.25 mg in the prophylaxis of postoperative nausea and vomiting after alfentanil-supplemented inhalation anaesthesia, Alon, E., *et al.*, (*ESA*) A.12

——, Pharmacokinetic behaviour of transdermal fentanyl, Van Bastelaere, M., *et al.*, (*ESA*) A.146

——, Pharmacokinetics and effects of i.m. alfentanil as premedication for outpatient cataract surgery, Ali-Melkkilä, T., *et al.*, (*ESA*) A.145

——, Propofol and alfentanil mixture, Sandin, R., (*C*) 382–383

——, Propofol and alfentanil mixture, Taylor, I. N., *et al.*, (*C*) 383

——, Propofol and alfentanil or thiopentone and suxamethonium for tracheal intubation, Beck, G. N., *et al.*, (*ARS*) 483P

——, Quality of induction: a clinical comparison of Etomidat-Lipuro® and Hypnomidate®, Wiebalck, A., *et al.*, (*ESA*) A.154

——, Total intravenous anaesthesia (TIVA) with propofol and alfentanil for renal transplantation, Kirvelä, M., *et al.*, (*ESA*) A.81

——, Tracheal intubation after induction of anaesthesia with propofol, alfentanil and i.v. lignocaine, Davidson, J. A. H., *et al.* 163–166

——, Use of alfentanil with propofol for nasotracheal intubation without neuromuscular block, Coghlan, S. F. E., *et al.* 89–91

Analgesics opioid, buprenorphine, Blended anaesthesia in pediatric major surgery: top-up *vs* epidural continuous infusion, Savoia, G., *et al.*, (*ESA*) A.159

——, Efficacy of postoperative pain treatment regimens using both buprenorphine and papaveretum sequentially after abdominal hysterectomy, Green, D. W., *et al.* 626–630

——, Fentanyl or buprenorphine side effects in spinal anaesthesia, Foppoli, R., *et al.*, (*ESA*) A.132

——, Safety of PCA in elderly, Santangelo, E., *et al.*, (*ESA*) A.206

Analgesics opioid, diamorphine, Diamorphine/bupivacaine mixture *vs* plain bupivacaine: a comparison of epidural infusions in labour, Bailey, C. R., *et al.*, (*ESA*) A.169

Analgesics opioid, fentanyl, A comparison of midazolam and midazolam plus fentanyl for colonoscopy, Dupont, H., *et al.*, (*ESA*) A.9

——, A continuous subdural block, Collier, C. B., *et al.* 462–465

——, Differential effects of alfentanil, fentanyl, pethidine and lignocaine administered intrathecally on nociceptive responses evoked by low and high frequency stimulation of somatic nerves, Wang, C., *et al.* 63–69

——, Does propofol supplemented anaesthesia affect neurophysiological outcome following cardiopulmonary bypass? Phillips, A. S., *et al.*, (*ARS*) 484P

——, Effect of fentanyl on [^{3}H]noradrenaline uptake in isolated neuronal cell preparations, Atcheson, R., *et al.*, (*ARS*) 485P

——, Effects of intrathecal meperidine (MP), fentanyl (FN) and lidocaine (LD) on somatosensory (SSEP) and cortical motor (CMEP) evoked potentials in humans, Fernandez, S., *et al.*, (*ESA*) A.119

——, Effects of morphine and its metabolites on opiate receptor binding and cyclic adenosine-3′,5′-monophosphate (cAMP) formation in human neuroblastoma cells, Lambert, D. G., *et al.*, (*ARS*) 475–476P

——, Fentanyl, as pethidine, inhibits post anaesthesia shivering, Alfonsi, P., *et al.*, (*ESA*) A.74

——, Fentanyl or buprenorphine side effects in spinal anaesthesia, Foppoli, R., *et al.*, (*ESA*) A.132
——, Intranasal fentanyl for breakthrough cancer pain or incident pain, Striebel, W. H., *et al.*, (*ESA*) A.210
——, Intranasal fentanyl for postoperative pain management in an unselected population, Striebel, W. H., *et al.*, (*ESA*) A.209
——, Patient-controlled extradural analgesia to compare bupivacaine, fentanyl and bupivacaine with fentanyl in the treatment of postoperative pain, Cooper, D. W., *et al.* 503–507
——, Pharmacokinetics of intranasal fentanyl, Striebel, H. W., *et al.*, (*ESA*) A.208
——, Pre-emptive analgesia, Dahl, J. B., *et al.*, (*C*) 379
——, Pre-emptive analgesia, Katz, J., *et al.*, (*C*) 378
——, Preoxygenation and Sp_{O_2} after induction of anaesthesia with propofol and fentanyl, Rittoo, D. B., *et al.*, (*ARS*) 486P
——, Propofol/fentanyl-anesthesia in patients with highly depressed cardiac function, Rauch, H., *et al.*, (*ESA*) A.30
——, Relative efficacy and potency of nalmefene, a long-acting opioid antagonist, Watson, N. A., *et al.*, (*ARS*) 479P
——, Subarachnoid anaesthesia (SAA) and postoperative analgesia with bupivacaine (BV) plus fentanyl (FN) in geriatric patients, Fernandez, D., *et al.*, (*ESA*) A.131
Analgesics opioid, methadone, Ventilatory effects of morphine, pethidine and methadone in children, Hamunen, K. 414–418
Analgesics opioid, morphine, Addition of droperidol to patient-controlled analgesia: effect on nausea and vomiting, Williams, O. A., *et al.*, (*ARS*) 479P
——, Addition of droperidol to PCA morphine: what is the optimal dose? Lamond, C. T., *et al.*, (*ESA*) A.204
——, Analgesia by wound infiltration before or after surgery in inguinal hernioraphy, Hennart, D., *et al.*, (*ESA*) A.202
——, Effect of morphine on a nociceptive flexion reflex in patients with postoperative pain, Chauvin, M., *et al.*, (*ESA*) A.115
——, Effects of morphine and its metabolites on opiate receptor binding and cyclic adenosine-3′,5′-monophosphate (cAMP) formation in human neuroblastoma cells, Lambert, D. G., *et al.*, (*ARS*) 475–476P
——, High dose oral morphine in cancer pain management, Radbruch, L., *et al.*, (*ESA*) A.212
——, Intra-articular morphine for pain relief after anterior cruciate ligament repair, Joshi, G. P., *et al.* 87–88
——, Intrathecal pain relief in terminally ill cancer patients at home, Wagemans, M. F. M., *et al.*, (*ESA*) A.213
——, Involvement of μ, δ, and κ receptors in the inhibition by intrathecal morphine of a C-fibre evoked reflex in the rat, Guirimand, F., *et al.*, (*ESA*) A.116
——, Ketorolac postoperative analgesia, Al-Hasani, A., (*C*) 112–113
——, Ketorolac postoperative analgesia, Kinsella, J., (*C*) 113
——, Pain relief after anterior cruciate ligament repair, Joshi, G. P., (*C*) 600
——, Pain relief for infants undergoing abdominal surgery: comparison of infusions of i.v. morphine and extradural bupivacaine, Wolf, A. R., *et al.* 10–16
——, Postoperative analgesia: a two dosage regimens trial for i.m. morphine after early i.v. titration, Butscher, K., *et al.*, (*ESA*) A.201
——, Postoperative hypoxaemia: comparison of epidural and patient controlled analgesia, Spencer, A., *et al.*, (*ESA*) A.207
——, Pre-emptive analgesia, Dahl, J. B., *et al.*, (*C*) 379
——, Pre-emptive analgesia, Katz, J., *et al.*, (*C*) 378
——, Preemptive analgesia with epidural morphine, Nègre, I., *et al.*, (*ESA*) A.203
——, Relative efficacy and potency of nalmefene, a long-acting opioid antagonist, Watson, N. A., *et al.*, (*ARS*) 479P
——, Safety of PCA in elderly, Santangelo, E., *et al.*, (*ESA*) A.206
——, The effect of parenteral diclofenac and morphine on efficacy duration and height of blockade during continuous epidural bupivacaine 0.5%, Forbes, D., *et al.*, (*ESA*) A.125
——, Treatment of cancer pain with morphine (MO)—A double blind study of extradural (ED) *versus* intramuscular (im) routes of administration, Nath, S., *et al.*, (*ESA*) A.211
——, Ventilatory effects of morphine, pethidine and methadone in children, Hamunen, K. 414–418
Analgesics opioid, morphine-3-glucuronide, Effects of morphine and its metabolites on opiate receptor binding and cyclic adenosine-3′,5′-monophosphate (cAMP) formation in human neuroblastoma cells, Lambert, D. G., *et al.*, (*ARS*) 475–476P
Analgesics opioid, morphine-6-glucuronide, Effects of morphine and its metabolites on opiate receptor binding and cyclic adenosine-3′,5′-monophosphate (cAMP) formation in human neuroblastoma cells, Lambert, D. G., *et al.*, (*ARS*) 475–476P
——, Morphine-6-glucuronide disposition in renal impairment, Hanna, M. H., *et al.* 511–514
Analgesics opioid, papaveretum, Efficacy of postoperative pain treatment regimens using both buprenorphine and papaveretum sequentially after abdominal hysterectomy, Green, D. W., *et al.* 626–630
Analgesics opioid, pethidine, A physiological model for the distribution of injected agents, with special reference to pethidine, Davis, N. R., *et al.* 248–258
——, Differential effects of alfentanil, fentanyl, pethidine and lignocaine administered intrathecally on nociceptive responses evoked by low and high frequency stimulation of somatic nerves, Wang, C., *et al.* 63–69
——, Effects of intrathecal meperidine (MP), fentanyl (FN) and lidocaine (LD) on somatosensory (SSEP) and cortical motor (CMEP) evoked potentials in humans, Fernandez, S., *et al.*, (*ESA*) A.119
——, Evaluation of the analgesic effect of metoclopramide after opioid-free analgesia, Lisander, B. 631–633
——, Fentanyl, as pethidine, inhibits post anaesthesia shivering, Alfonsi, P., *et al.*, (*ESA*) A.74
——, Propofol anaesthesia with spontaneous breathing for extracorporeal shock wave lithotripsy, Pasch, T., *et al.*, (*ESA*) A.153
——, Ventilatory effects of morphine, pethidine and methadone in children, Hamunen, K. 414–418
Analgesics opioid, sufentanil, Echocardiographic study of the induction with a low-dose of sufentanil for coronary artery surgery, Bromberg, N., *et al.*, (*ESA*) A.28
——, Patient controlled epidural analgesia *vs* intermittent injections during labor using 0.125% bupivacaine and sufentanil, Baudot, J., *et al.*, (*ESA*) A.170
——, Sufentanil first-pass pulmonary uptake at three different steady state concentrations of the drug, Boer, F., *et al.*, (*ESA*) A.147
——, Sufentanil increases intracranial pressure in patients with head trauma, Albanese, J., *et al.*, (*ESA*) A.107
Anatomy, jugular vein, Use of ultrasound to evaluate internal jugular vein anatomy and to facilitate central venous cannulation in paediatric patients, Alderson, P. J., *et al.* 145–148
Anesthésie et Analgésie en Obstétrique. Collection d'Anesthésiologie et de Réanimation, Vol. 33, Schoeffler, P., (editor), (*R*) 708
Antacids, metoclopramide, Comparison of ondansetron, metoclopramide and droperidol for the prophylaxis of emetic symptoms after gynecological laparoscopic procedures, Geiger, C., *et al.*, (*ESA*) A.14
——, Pain on i.v. injection of metoclopramide, Wilkinson, D. J., (*C*) 239
Antagonists benzodiazepine, flumazenil, Flumazenil facilitates intraoperative arousal in scoliosis surgery, Koscielniak-Nielsen, Z. J., *et al.*, (*ESA*) A.157
——, Pharmacokinetics of flumazenil and midazolam, Jones, R. D. M., *et al.* 286–292
Antagonists benzodiazepine, Ro 15-4513, Nitrous oxide induced neuronal depression: modification through benzodiazepine receptors, Dzoljic, M., *et al.*, (*ESA*) A.112
Antagonists miscellaneous, Comparison of ondansetron, metoclopramide and droperidol for the prophylaxis of emetic symptoms after gynecological laparoscopic procedures, Geiger, C., *et al.*, (*ESA*) A.14
——, Double-blind comparison of ondansetron, droperidol and saline for prevention of nausea & vomiting after orthopaedic surgery, Gan, T. J., *et al.*, (*ESA*) A.13
——, Ondansetron 4 mg *vs* droperidol 1.25 mg in the prophylaxis of postoperative nausea and vomiting after alfentanil-supplemented inhalation anaesthesia, Alon, E., *et al.*, (*ESA*) A.12
——, Partial reversal of the effects of extradural clonidine by oral yohimbine in postoperative patients, Liu, N., *et al.* 515–518
Antagonists neuromuscular block, edrophonium, Neostigmine and edrophonium antagonism of moderate neuromuscular block induced by pancuronium or tubocurarine, Shorten, G. D., *et al.* 160–162
Antagonists neuromuscular block, neostigmine, Neostigmine and edrophonium antagonism of moderate neuromuscular block induced by pancuronium or tubocurarine, Shorten, G. D., *et al.* 160–162
——, Neostigmine antagonism of neuromuscular blockade induced by mivacurium, vecuronium and atracurium, Dernovoi, B. S., *et al.*, (*ESA*) A.137

——, Prejunctional action of neostigmine on mouse neuromuscular preparations, Braga, M. F. M., *et al.* 405–410

——, Reversal of vecuronium induced neuromuscular blockade: no effects of atropine administration timing, Baurain, M. J., *et al.*, (*ESA*) A.134

Antagonists opioid, miscellaneous, Differential effects of specific delta and kappa opioid antagonists on the bidirectionnal effect of naloxone in arthritic rats, Cattaneo, I., *et al.*, (*ESA*) A.114

——, Involvement of μ, δ, and κ receptors in the inhibition by intrathecal morphine of a C-fibre evoked reflex in the rat, Guirimand, F., *et al.*, (*ESA*) A.116

Antagonists opioid, nalmefene, Relative efficacy and potency of nalmefene, a long-acting opioid antagonist, Watson, N. A., *et al.*, (*ARS*) 479P

Antagonists opioid, naloxone, Differential effects of specific delta and kappa opioid antagonists on the bidirectionnal effect of naloxone in arthritic rats, Cattaneo, I., *et al.*, (*ESA*) A.114

——, Relative efficacy and potency of nalmefene, a long-acting opioid antagonist, Watson, N. A., *et al.*, (*ARS*) 479P

Antibiotics, External ventricular CSF drains infections, Mahé, V., *et al.*, (*ESA*) A.109

Anti-cardiolipin antibody syndrome, Anaesthetic implications of the anti-cardiolipin antibody syndrome, Menon, G., *et al.* 587–590

Arterial pressure, drug effects, Mechanisms of ECG changes during Caesarean section (CS)—a hypothesis, Svanström, M., *et al.*, (*ESA*) A.177

Arterial pressure, hypertension, aspirin, Aspirin, bleeding time and central neural block, Wildsmith, J. A. W., *et al.*, (*C*) 112

Arterial pressure, hypotension, Adrenaline-induced hypotension in neurosurgery, Phillips, S., *et al.* 687–688

——, Prevention and treatment of hypotension during central neural block, McCrae, A. F., *et al.* 672–680

Arterial pressure, measurement, Clinical evaluation of the calibration of noninvasive continuous blood pressure measurement devices by means of oscillometric blood pressure measurements, de Jong, J. R., *et al.*, (*ESA*) A.15

——, Comparison of automatic oscillometric arterial pressure measurement with conventional auscultatory measurement in the labour ward, Hasan, M. A., *et al.* 141–144

Assessment, preanaesthetic, Antepartum assessment for anaesthesia, Cody, M., *et al.*, (*C*) 116

——, Antepartum assessment for anaesthesia, Reynolds, F., (*C*) 116

——, Antepartum assessment for anaesthesia, Uncles, D. R., *et al.*, (*C*) 116

——, Logistic regression analysis of fixed patient factors for postoperative sickness: a model for risk assessment, Palazzo, M., *et al.* 135–140

Biotransformation (drug), anaesthetics volatile, Hepatotoxicity of volatile anaesthetics, Elliott, R. H., *et al.* 339–348

Biotransformation (drug), diazepam, Hepatic elimination of diazepam: interactions with albumin, desflurane and sevoflurane, Dale, O., *et al.* 454–455

Blood, anaesthetic concentration, Determination of a pharmacokinetic model for propofol induction of anaesthesia, Viviand, X., *et al.*, (*ESA*) A.150

——, Pharmacokinetics of propofol administered by infusion in dogs undergoing surgery, Nolan, A., *et al.* 546–551

——, Target-controlled intravenous sedation with propofol, Mergaert, C., *et al.*, (*ESA*) A.149

Blood, anticoagulants, aspirin, Inhibition of increase of blood thromboxane concentration by acetylsalicylic acid after release of tourniquet in lower extremity operations, Ojanen, R., *et al.*, (*ESA*) A.94

Blood, chemotaxis, Propofol decreases random and chemotactic stimulated locomotion of human neutrophils *in vitro*, Jensen, A. G., *et al.* 99–100

Blood, coagulation, Anaesthesia affects plasma concentrations of vasopressin, von Willebrand factor and coagulation factor VIII in cardiac surgical patients, Kuitunen, A., *et al.* 173–180

——, Aprotinin does not decrease surgical bleeding and could promote arterial thrombosis in the pig: a prospective randomized, blind, study, Samama, C. M., *et al.*, (*ESA*) A.100

——, Aspirin, bleeding time and central neural block, Wildsmith, J. A. W., *et al.*, (*C*) 112

——, Blood requirements reduction in orthotopic liver transplantation with aprotinin, Monedero, P., *et al.*, (*ESA*) A.98

——, Haemostasis and thrombelastography: a cautious note, Gupta, N. K., *et al.*, (*C*) 699

——, Haemostasis and thrombelastography: a cautious note, Mallett, S. V., *et al.*, (*C*) 699–700

——, High dose aprotinin *versus* desmo-pressin acetate treatment in cardiac surgery, Hidalgo, F., *et al.*, (*ESA*) A.99

——, The combined prophylactic administration of H1 and H2 receptor blockers in the prevention of protamine related haemodynamic effects and the relation between antihistaminics-leucocytes and pulmonary vascular resistance, Durak, P., *et al.*, (*ESA*) A.95

——, The haemostatic response to surgery and trauma, Murphy, W. G., *et al.* 205–213

——, The relationship between cardiopulmonary bypass related immunologic effects and complement, thromboxane and leucocyte parameters, Durak, P., *et al.*, (*ESA*) A.96

——, Use of aprotinine during cytoreductive surgery of ovarian cancer, Lequeau, F., *et al.*, (*ESA*) A.97

Blood, erythrocytes, The role of recombinant growth factors in transfusion medicine, Goodnough, L. T. 80–86

Blood, flow, The haemostatic response to surgery and trauma, Murphy, W. G., *et al.* 205–213

Blood, flow, feto-uteroplacental, Incremental spinal anaesthesia for elective Caesarean section: maternal and fetal haemodynamic effects, Robson, S. C., *et al.* 634–638

Blood, flow, forearm, Comparison of the onset of depolarizing *vs* non-depolarizing block after early tourniquet release in the isolated forearm, Hood, J. R., *et al.*, (*ARS*) 480P

——, Recovery of atracurium and vecuronium neuromuscular block in the isolated forearm, Law Min, J.-C., *et al.*, (*ARS*) 480–481P

Blood, flow, skin, Effects of intradermal lignocaine and mepivacaine on human cutaneous circulation in areas with histamine-induced neurogenic inflammation, Fruhstorfer, H., *et al.* 167–172

Blood, glucose, Neonatal glycemia: does the maternal i.v. fluid regimen during labor make a difference? Menigaux, C., *et al.*, (*ESA*) A.175

Blood, haematopoiesis, Effects of recombinant-human erythropoietin on postoperative transfusion requirements in subjects undergoing major orthopaedic surgery, Faris, P. P., *et al.*, (*ESA*) A.101

——, The role of recombinant growth factors in transfusion medicine, Goodnough, L. T. 80–86

Blood, haemodialysis, Morphine-6-glucuronide disposition in renal impairment, Hanna, M. H., *et al.* 511–514

Blood, haemodilution, Effect of selective cell separation on respiratory function after aortic aneurysm surgery, McKavney, M., *et al.*, (*ARS*) 475P

——, Perioperative blood loss, Appadu, B., (*C*) 492–493

Blood, haemofiltration, Mortality in ITU patients receiving neuromuscular blocking drugs, Hunter, J. M., *et al.*, (*C*) 238–239

Blood, haemolysis, Does etomidate cause haemolysis? Doenicke, A., *et al.*, (*C*) 491

——, Does etomidate cause haemolysis? Wertz, E., (*C*) 490–491

Blood, leucocytes, Effects of diazepam additives on the mononuclear phagocytic system, Catalá, J. C., *et al.*, (*ESA*) A.89

——, Platelet serotonin is a mediator potentially involved in anaphylactic reaction to neuromuscular blocking drugs, Bermejo, N., *et al.* 322–325

——, The combined prophylactic administration of H1 and H2 receptor blockers in the prevention of protamine related haemodynamic effects and the relation between antihistaminics-leucocytes and pulmonary vascular resistance, Durak, P., *et al.*, (*ESA*) A.95

——, The relationship between cardiopulmonary bypass related immunologic effects and complement, thromboxane and leucocyte parameters, Durak, P., *et al.*, (*ESA*) A.96

Blood, loss, Adrenaline-induced hypotension in neurosurgery, Phillips, S., *et al.* 687–688

——, Aprotinin does not decrease surgical bleeding and could promote arterial thrombosis in the pig: a prospective randomized, blind, study, Samama, C. M., *et al.*, (*ESA*) A.100

——, Blood loss during total hip replacement, Jones, N. O., *et al.*, (*C*) 235–236

——, Blood loss during total hip replacement, McSwiney, M., (*C*) 236

——, Blood requirements reduction in orthotopic liver transplantation with aprotinin, Monedero, P., *et al.*, (*ESA*) A.98

——, High dose aprotinin *versus* desmo-pressin acetate treatment in cardiac surgery, Hidalgo, F., *et al.*, (*ESA*) A.99

——, Perioperative blood loss, Appadu, B., (*C*) 492–493

——, Perioperative blood loss, Smith, G., (*C*) 493

——, The effects of bupivacaine, mepivacaine and prilocaine on platelet aggregation, Bayhan, N., *et al.*, (*ESA*) A.123
——, Use of aprotinine during cytoreductive surgery of ovarian cancer, Lequeau, F., *et al.*, (*ESA*) A.97
Blood, neutrophils, Benzodiazepines and their solvents influence neutrophil granulocyte function, Weiss, M., *et al.* 317–321
——, Effect of propofol on neutrophil respiratory burst, Ogilvy, A. J., *et al.*, (*ARS*) 476P
——, Propofol decreases random and chemotactic stimulated locomotion of human neutrophils *in vitro*, Jensen, A. G., *et al.* 99–100
Blood, platelets, Acute preoperative plasmapheresis during cardiac surgery, Armellin, G., *et al.*, (*ESA*) A.104
——, Platelet serotonin is a mediator potentially involved in anaphylactic reaction to neuromuscular blocking drugs, Bermejo, N., *et al.* 322–325
——, The effects of bupivacaine, mepivacaine and prilocaine on platelet aggregation, Bayhan, N., *et al.*, (*ESA*) A.123
——, The role of recombinant growth factors in transfusion medicine, Goodnough, L. T. 80–86
Blood, replacement, Acute preoperative plasmapheresis during cardiac surgery, Armellin, G., *et al.*, (*ESA*) A.104
——, Blood requirements reduction in orthotopic liver transplantation with aprotinin, Monedero, P., *et al.*, (*ESA*) A.98
——, Effects of plasma volume substitution on right ventricle volumes and function using Elohes® and Plasmion®, Lepage, J. Y., *et al.*, (*ESA*) A.35
——, Effects of recombinant-human erythropoietin on postoperative transfusion requirements in subjects undergoing major orthopaedic surgery, Faris, P. P., *et al.*, (*ESA*) A.101
——, High dose aprotinin *versus* desmo-pressin acetate treatment in cardiac surgery, Hidalgo, F., *et al.*, (*ESA*) A.99
——, Hypertonic solutions in acute massive haemorrhage, Brimacombe, J., *et al.*, (*C*) 705
——, Hypertonic solutions in acute massive haemorrhage, Park, G. R., (*C*) 706
——, Preoperative autotransfusion in emergency surgery for spine trauma, Riou, B., *et al.*, (*ESA*) A.102
——, Volume replacement with hydroxyethyl starch solution in children, Boldt, J., *et al.* 661–665
Blood, salvage, Acute preoperative plasmapheresis during cardiac surgery, Armellin, G., *et al.*, (*ESA*) A.104
——, Effects of postoperative auto-transfusion in spine surgery, Riou, B., *et al.*, (*ESA*) A.103
——, Preoperative autotransfusion in emergency surgery for spine trauma, Riou, B., *et al.*, (*ESA*) A.102
Blood, transfusion, Blood loss during total hip replacement, Jones, N. O., *et al.*, (*C*) 235–236
——, Blood loss during total hip replacement, McSwiney, M., (*C*) 236
——, Hypertonic solutions in acute massive haemorrhage, Brimacombe, J., *et al.*, (*C*) 705
——, Hypertonic solutions in acute massive haemorrhage, Park, G. R., (*C*) 706
Blood, volume, A comparison between various hemodynamic parameters reflecting preload during graded hemorrhage in ventilated dogs, Preisman, S., *et al.*, (*ESA*) A.51
——, Effects of plasma volume substitution on right ventricle volumes and function using Elohes® and Plasmion®, Lepage, J. Y., *et al.*, (*ESA*) A.35
——, Glycine and its metabolites during and after intrauterine YAG laser surgery, Van Boven, M. J., *et al.*, (*ESA*) A.87
——, Hypertonic solutions in acute massive haemorrhage, Brimacombe, J., *et al.*, (*C*) 705
——, Hypertonic solutions in acute massive haemorrhage, Park, G. R., (*C*) 706
——, Prevention and treatment of hypotension during central neural block, McCrae, A. F., *et al.* 672–680
——, Prevention of acute tubular necrosis by volume loading in kidney transplantation, Mouquet, C., *et al.*, (*ESA*) A.82
——, Propofol/fentanyl-anesthesia in patients with highly depressed cardiac function, Rauch, H., *et al.*, (*ESA*) A.30
——, The systolic pressure variation predicts response to volume loading in patients ventilated after aortic surgery, Coriat, P., *et al.*, (*ESA*) A.38
——, Use of transoesophageal echocardiography to manage beta-adrenoceptor block and assess left ventricular function in a patient with phaeochromocytoma, Ryan, T., *et al.* 101–103
——, Volume loading and hormonal factors in the prevention of acute tubular necrosis in kidney transplantation, Mouquet, C., *et al.*, (*ESA*) A.83
——, Volume replacement with hydroxyethyl starch solution in children, Boldt, J., *et al.* 661–665
Book Reviews
ABC of Transfusion, 2nd Edn, Contreras, M., (editor), (*R*) 495
Adult Respiratory Distress Syndrome, Artigas, A., *et al.*, (editors), (*R*) 117
Anaesthesia Review 9, Kaufman, L., (editor), (*R*) 385
Anesthésie et Analgésie en Obstétrique. Collection d'Anesthésiologie et de Réanimation, Vol. 33, Schoeffler, P., (editor), (*R*) 708
British Medical Bulletin: A Series of Expert Reviews. Pain, Mechanisms and Management, Wells, J. C. D., *et al.*, (editors), (*R*) 495
Collection d'Anesthésiologie et de Réanimation, Volume 30: Monitorage Non-Invasif en Réanimation, Annat, G., *et al.*, (editors), (*R*) 117
Conduction Blockade for Postoperative Analgesia: Mechanisms and Management, McClure, J. H., *et al.*, (editors), (*R*) 239
Electrical Trauma: the Pathophysiology, Manifestations and Clinical Management, Lee, R. C., *et al.*, (editors), (*R*) 601
Essay Plans for Anaesthesia Exams, Michel, M. Z., *et al.*, (*R*) 709
Handbook of Percutaneous Central Venous Catheterisation, 2nd Edn, Rosen, M., *et al.*, (editors), (*R*) 601
Hyperalgesia and Allodynia, Willis, W., (editor), (*R*) 385
Hypoxia, Metabolic Acidosis and the Circulation, Arieff, A. I., (editor), (*R*) 118
Key Topics in Anaesthesia, Craft, T. M., *et al.*, (editors), (*R*) 117
Management of Acute Pain: A Practical Guide, Ready, L. B., *et al.*, (editors), (*R*) 495
MCQs in Anaesthesia: Basic Sciences, Kumar, B., (editor), (*R*) 117
Medical Writing: A Prescription for Clarity, Goodman, N., *et al.*, (editors), (*R*) 385
Moving to Audit, An Educational Package for Hospital Doctors and General Practitioners, Arnold, C., *et al.* 118
Principles and Protocols in Intensive Care, Willatts, S. M., *et al.*, (editors), (*R*) 239
Specialty Medical Audit (Medical Audit Series 4), Shaw, C., (*R*) 495
Techniques in Extracorporeal Circulation, 3rd Edn, Kay, P. H., (editor), (*R*) 239–240
The Complete Recovery Room Book, Hatfield, A., *et al.*, (*R*) 709
The Oxford Textbook of Clinical Pharmacology and Drug Therapy, 2nd Edn, Graham-Smith, D. G., *et al.*, (*R*) 601
Transesophageal Echocardiography, Clements, F. M., *et al.*, (editors), (*R*) 708
Ward's Anaesthetic Equipment, 3rd Edn, Davey, A., *et al.*, (*R*) 240
Brain, blood flow, Cerebral blood flow velocities (CBFV) during anaesthesia for gynaecological laparoscopic surgery, Granry, J. C., *et al.*, (*ESA*) A.32
——, Cerebral perfusion during obstructive sleep apnea (OSA), Bålfors, E., *et al.*, (*ESA*) A.62
——, EEG-monitoring during defibrillator-implantation: effects of repetitive cerebral ischemia on electric brain activity, Spies, C., *et al.*, (*ESA*) A.110
——, Effect of nitrous oxide on cerebral blood flow in normal humans, Field, L. M., *et al.* 154–159
——, Midazolam prevents ketamine-induced stimulation of cerebral metabolism, Åkeson, J., *et al.*, (*ESA*) A.111
——, Sufentanil increases intracranial pressure in patients with head trauma, Albanese, J., *et al.*, (*ESA*) A.107
——, The choice of ECM rate could improve the neuroprotection during CPR, Iannuzzi, E., *et al.*, (*ESA*) A.195
——, Transcranial Doppler sonography: effect of propofol and thiopental in patients with brain tumors and brain injuries, Schregel, W., *et al.*, (*ESA*) A.105
Brain, central monoamines, Effects of midazolam and flunitrazepam on the release of dopamine from rat striatum measured by *in vivo* microdialysis, Takada, K., *et al.* 181–185
Brain, electroencephalography, Closed-loop feedback controlled administration of alfentanil during alfentanil–nitrous oxide anaesthesia, Schwilden, H., *et al.* 389–393
——, EEG-monitoring during defibrillator-implantation: effects of repetitive cerebral ischemia on electric brain activity, Spies, C., *et al.*, (*ESA*) A.110
——, Nitrous oxide-mediated activation of the EEG during isoflurane anaesthesia in patients, Yli-Hankala, A., *et al.* 54–57
Brain, evoked potentials, Accuracy of processed auditory evoked response in predicting movement during cardiac surgery, Kuppe, H., *et al.*, (*ESA*) A.31

——, Effect of nitrous oxide on auditory evoked potentials, Jessop, J., *et al.*, (*C*) 380
——, Effect of nitrous oxide on auditory evoked potentials, Plourde, G., (*C*) 379–380
——, Effects of intrathecal meperidine (MP), fentanyl (FN) and lidocaine (LD) on somatosensory (SSEP) and cortical motor (CMEP) evoked potentials in humans, Fernandez, S., *et al.*, (*ESA*) A.119
——, Nitrous oxide induced neuronal depression: modification through benzodiazepine receptors, Dzoljic, M., *et al.*, (*ESA*) A.112
——, Validation of coherent frequency of the EEG as a measure of consciousness during anaesthesia, Munglani, R., *et al.*, (*ARS*) 483–484P
Brain, GABA, Dexmedetomidine does not exercise its anesthetic action through GABA, Salonen, M., *et al.*, (*ESA*) A.113
——, Effects of midazolam and flunitrazepam on the release of dopamine from rat striatum measured by *in vivo* microdialysis, Takada, K., *et al.* 181–185
Brain, injury, Transcranial Doppler sonography: effect of propofol and thiopental in patients with brain tumors and brain injuries, Schregel, W., *et al.*, (*ESA*) A.105
Brain, intracranial pressure, Effect of esmolol *versus* lidocaine on intracranial pressure and haemodynamic responses to laryngoscopy and intubation, Samaha, T., *et al.*, (*ESA*) A.118
——, Jugular bulb metabolic monitoring during hyperventilation in severe head trauma patients, De Deyne, C., *et al.*, (*ESA*) A.106
——, Sufentanil increases intracranial pressure in patients with head trauma, Albanese, J., *et al.*, (*ESA*) A.107
Brain, ischaemia, EEG-monitoring during defibrillator-implantation: effects of repetitive cerebral ischemia on electric brain activity, Spies, C., *et al.*, (*ESA*) A.110
——, Jugular bulb metabolic monitoring during hyperventilation in severe head trauma patients, De Deyne, C., *et al.*, (*ESA*) A.106
Brain, metabolism, Midazolam prevents ketamine-induced stimulation of cerebral metabolism, Åkeson, J., *et al.*, (*ESA*) A.111
Brain, saccadic eye movements, Evaluation of saccadic eye movements as an objective test during recovery from anesthesia, Paut, O., *et al.*, (*ESA*) A.10
British Medical Bulletin: A Series of Expert Reviews. Pain, Mechanisms and Management, Wells, J. C. D., *et al.*, (editors), (*R*) 495
Burkitt's lymphoma, Is Burkitt's lymphoma an etiology or a differential diagnosis of malignant hyperthermia? Lienhart, A., *et al.*, (*ESA*) A.93
Burns, Electrode burns during local hyperthermia, Stott, D. G., *et al.* 370–371

Calcium channel block, nicardipine, Does nicardipine potentiate the neuromuscular block of atracurium? Bazin, J. E., *et al.*, (*ESA*) A.136
Calcium channel block, nifedipine, Effect of premedication with nifedipine on intraoperative hypothermia, Vassilieff, N., *et al.*, (*ESA*) A.71
Calcium channel block, ryanodine, Comparison of *in vitro* contracture testing with ryanodine, halothane and caffeine in malignant hyperthermia and other neuromuscular disorders, Hopkins, P. M., *et al.* 397–401
Cancer, Electrode burns during local hyperthermia, Stott, D. G., *et al.* 370–371
——, High dose oral morphine in cancer pain management, Radbruch, L., *et al.*, (*ESA*) A.212
——, Intranasal fentanyl for breakthrough cancer pain or incident pain, Striebel, W. H., *et al.*, (*ESA*) A.210
——, Intrathecal pain relief in terminally ill cancer patients at home, Wagemans, M. F. M., *et al.*, (*ESA*) A.213
——, Is Burkitt's lymphoma an etiology or a differential diagnosis of malignant hyperthermia? Lienhart, A., *et al.*, (*ESA*) A.93
——, Postoperative hypoxaemia: comparison of epidural and patient controlled analgesia, Spencer, A., *et al.*, (*ESA*) A.207
——, Transcranial Doppler sonography: effect of propofol and thiopental in patients with brain tumors and brain injuries, Schregel, W., *et al.*, (*ESA*) A.105
——, Treatment of cancer pain with morphine (MO)—A double blind study of extradural (ED) *versus* intramuscular (im) routes of administration, Nath, S., *et al.*, (*ESA*) A.211
——, Use of aprotinine during cytoreductive surgery of ovarian cancer, Lequeau, F., *et al.*, (*ESA*) A.97
Carbon dioxide, measurement, Relationship between arterial $P\mathrm{CO_2}$ ($Pa_{\mathrm{CO_2}}$) and end tidal $\mathrm{CO_2}$ ($\mathrm{ETCO_2}$) recorded through a laryngeal mask (LMA) in children breathing spontaneously, Van Obbergh, L. J., *et al.*, (*ESA*) A.164
Carbon dioxide, partial pressure, An alternative method of increasing $P\mathrm{CO_2}$ using apnoea and continuous positive airway pressure, Karlsten, R., *et al.* 411–413
——, Is correlation of arterial and end-tidal carbon dioxide pressure during inhalation anaesthesia better with laryngeal mask as compared to face mask? Ivens, D., *et al.*, (*ESA*) A.17
——, Relationship between arterial $P\mathrm{CO_2}$ ($Pa_{\mathrm{CO_2}}$) and end tidal $\mathrm{CO_2}$ ($\mathrm{ETCO_2}$) recorded through a laryngeal mask (LMA) in children breathing spontaneously, Van Obbergh, L. J., *et al.*, (*ESA*) A.164
——, Respiratory effects of laparoscopic cholecystectomy (preliminary data), Crea, M. A., *et al.*, (*ESA*) A.63
Carbon dioxide, rebreathing, Fresh gas requirements of an enclosed afferent reservoir breathing system in anaesthetized, spontaneously breathing adults, Barrie, J. R., *et al.* 468–470
Cardiorespiratory system, effects, Abdominal wall retraction may decrease anaesthesiological risks of laparoscopic cholecystectomy, Vereczkey, Z., *et al.*, (*ESA*) A.64
——, Diaphragmatic function after bupivacaine cervical extradural analgesia for chronic pain therapy, Nyström, E., *et al.*, (*ESA*) A.65
——, Pulmonary and systemic vascular effects of isoproterenol, nitroglycerin and prostaglandin E1 early after cardiac operations in patients with pulmonary hypertension, Alvarez, J., *et al.*, (*ESA*) A.27
——, Respiratory effects of laparoscopic cholecystectomy (preliminary data), Crea, M. A., *et al.*, (*ESA*) A.63
——, The combined prophylactic administration of H1 and H2 receptor blockers in the prevention of protamine related haemodynamic effects and the relation between antihistaminics-leucocytes and pulmonary vascular resistance, Durak, P., *et al.*, (*ESA*) A.95
Cardiovascular system, effects, Cardiovascular effects of a pancuronium–vecuronium mixture, Doyle, M., *et al.*, (*ARS*) 486–487P
——, Cardiovascular effects of i.v. induction in children: comparison between propofol and thiopentone, Aun, C. S. T., *et al.* 647–653
——, Does exogenous dopamine reverse cardiovascular depression induced by isoflurane during thoracic epidural blockade? Raner, C., *et al.*, (*ESA*) A.49
——, Effects of nitrous oxide (N_2O) on systemic haemodynamics, regional left ventricular (LV) function and incidence of myocardial ischaemia (MI) in vascular surgical patients with coronary artery disease (CAD), Hohner, P., *et al.*, (*ESA*) A.41
——, Local *versus* neurogenic vasodilator effects of desflurane and isoflurane in the small intestine, Sundeman, H., *et al.*, (*ESA*) A.50
Cardiovascular system, responses, Anaesthesia affects plasma concentrations of vasopressin, von Willebrand factor and coagulation factor VIII in cardiac surgical patients, Kuitunen, A., *et al.* 173–180
——, Comparison of dobutamine with enoximone following open heart surgery in small children, Innes, P., *et al.*, (*ESA*) A.167
——, Differential effects of alfentanil, fentanyl, pethidine and lignocaine administered intrathecally on nociceptive responses evoked by low and high frequency stimulation of somatic nerves, Wang, C., *et al.* 63–69
——, Dose dependent effects of oral medication with midazolam, Biro, P., *et al.*, (*ESA*) A.156
——, Echocardiographic study of the induction with a low-dose of sufentanil for coronary artery surgery, Bromberg, N., *et al.*, (*ESA*) A.28
——, Effect of esmolol *versus* lidocaine on intracranial pressure and haemodynamic responses to laryngoscopy and intubation, Samaha, T., *et al.*, (*ESA*) A.118
——, Effects of oral preoperative guanfacine on anesthetics requirements, Engelman, E., *et al.*, (*ESA*) A.144
——, Evaluation of cardiac function in ICU: right heart catheterization *vs* transesophageal echocardiography. Preliminary results, Vivien, B., *et al.*, (*ESA*) A.183
——, Haemodynamic and catecholamine responses to induction of anaesthesia and tracheal intubation: comparison between propofol and thiopentone, Lindgren, L., *et al.* 306–310
——, Haemodynamic and metabolic consequences of aortic occlusion during abdominal aortic surgery, Whalley, D. G., *et al.* 96–98
——, Haemodynamic changes in patients undergoing laparoscopic cholecystectomy: measurement by transthoracic electrical bioimpedance, Critchley, L. A. H., *et al.* 681–683

——, Haemodynamic changes produced by inhalation anaesthetics in the presence of phosphodiesterase inhibition, Molter, G., *et al.* 428–433
——, Influence of pneumoperitoneum and posture on hemodynamic and stress responses during anaesthesia for laparoscopic surgery, Odeberg, S., *et al.*, (*ESA*) A.34
——, Metabolic effects of propofol and flunitrazepam given for sedation after aortic surgery, Moritz, F., *et al.* 451–453
——, Prevention of acute tubular necrosis by volume loading in kidney transplantation, Mouquet, C., *et al.*, (*ESA*) A.82
——, Propofol and alfentanil or thiopentone and suxamethonium for tracheal intubation, Beck, G. N., *et al.*, (*ARS*) 483P
——, The pressor response to venous cannulation: attenuation by prior infiltration with local anaesthetic, Langham, B. T., *et al.* 519–521
——, Tolerance of preoperative transesophageal echocardiography in patients scheduled for aortic surgery, Gosgnach, M., *et al.*, (*ESA*) A.21
——, Use of alfentanil with propofol for nasotracheal intubation without neuromuscular block, Coghlan, S. F. E., *et al.* 89–91
Cat, Does etomidate cause haemolysis? Doenicke, A., *et al.*, (*C*) 491
——, Does etomidate cause haemolysis? Wertz, E., (*C*) 490–491
——, Local *versus* neurogenic vasodilator effects of desflurane and isoflurane in the small intestine, Sundeman, H., *et al.*, (*ESA*) A.50
——, Veterinary use of "Xylocaine" spray, Taylor, P. M., (*C*) 113
Cerebrospinal fluid, External ventricular CSF drains infections, Mahé, V., *et al.*, (*ESA*) A.109
Children, Clonidine in paediatric caudal anaesthesia, Jamali, S., *et al.*, (*ESA*) A.160
——, Comparison of dobutamine with enoximone following open heart surgery in small children, Innes, P., *et al.*, (*ESA*) A.167
——, Comparison of recovery from anaesthesia induced in children with either propofol or thiopentone, Runcie, C. J., *et al.* 192–195
——, Continuous monitoring of Sp_{O_2} during total intravenous anaesthesia with ketamine and spontaneous ventilation, Joly, L.-M., *et al.*, (*ESA*) A.58
——, Evaluation of the efficacy of forced-air warmer (Bair Hugger) during spinal surgery in children, Murat, I., *et al.*, (*ESA*) A.165
——, I.v. anaesthesia with propofol using a target-controlled infusion system: comparison with inhalation anaesthesia for general surgical procedures in children, Doyle, E., *et al.* 542–555
——, Metabolic effects of corrective surgery in infants and children with congenital heart defects, Puhakka, K., *et al.* 149–153
——, Neuromuscular blockade following mivacurium in children during N_2O–halothane, Orliaguet, G., *et al.*, (*ESA*) A.163
——, Pharmacokinetics of flumazenil and midazolam, Jones, R. D. M., *et al.* 286–292
——, Plasma concentrations of midazolam after i.v., nasal or rectal administration in children, Malinovsky, J.-M., *et al.* 617–620
——, Postoperative analgesia in children, Fell, D., (*E*) 4–5
——, Preoperative drinking and gastric contents, Mather, C., (*C*) 702
——, Preoperative drinking and gastric contents, Strunin, L., (*C*) 702
——, Propofol for tracheal intubation in paediatric outpatient anaesthesia, Montasser, A. M., (*ESA*) A.161
——, Relationship between arterial $P\mathrm{CO}_2$ (Pa_{CO_2}) and end tidal CO_2 ($\mathrm{ET}\mathrm{CO}_2$) recorded through a laryngeal mask (LMA) in children breathing spontaneously, Van Obbergh, L. J., *et al.*, (*ESA*) A.164
——, The laryngeal mask airway in paediatric practice, Wilson, I. G., (*E*) 124–125
——, The pharmacokinetics of rocuronium in pediatric patients: a pooled data analysis, Meistelman, C., *et al.*, (*ESA*) A.138
——, Use of thoracic epidural block for perioperative analgesia in children, Entress, A. H., *et al.*, (*ESA*) A.158
——, Ventilatory effects of morphine, pethidine and methadone in children, Hamunen, K. 414–418
——, Volume replacement with hydroxyethyl starch solution in children, Boldt, J., *et al.* 661–665
Collection d'Anesthésiologie et de Réanimation, Volume 30: Monitorage Non-Invasif en Réanimation, Annat, G., *et al.*, (editors), (*R*) 117
Complications, accidents, Evaluation of systematic TEE in patients suspected of blunt chest trauma, Catoire, P., *et al.*, (*ESA*) A.192
——, Jugular bulb metabolic monitoring during hyperventilation in severe head trauma patients, De Deyne, C., *et al.*, (*ESA*) A.106
——, Sufentanil increases intracranial pressure in patients with head trauma, Albanese, J., *et al.*, (*ESA*) A.107
——, The part of rescue helicopters in large accidents and disasters, Wenker, O., (*ESA*) A.197
Complications, acetonaemia, Accumulation of acetone in blood during long-term anaesthesia with closed systems, Strauß, J. M., *et al.* 363–364
Complications, adult respiratory distress syndrome, Adult respiratory distress syndrome after attempted strangulation, Murphy, P. G., *et al.* 583–586
——, Histology aspects of pulmonary barotrauma in critically ill patients with acute respiratory failure, Rouby, J. J., *et al.*, (*ESA*) A.181
——, IVOX, Skoyles, J., *et al.*, (*E*) 603–604
——, Non invasive monitoring of CO_2 in patients with septic shock, Bodin, L., *et al.*, (*ESA*) A.191
——, Surfactant and adult respiratory distress syndrome, Jacobson, W., *et al.* 522–526
Complications, alcohol abuse, Carbohydrate deficient transferrin: a new copredictor of alcoholism related postoperative complications? Heil, T., *et al.*, (*ESA*) A.88
——, Delayed presentation of an extradural abscess in a patient with alcohol abuse, Nordström, O., *et al.* 368–369
Complications, anaphylaxis, Platelet serotonin is a mediator potentially involved in anaphylactic reaction to neuromuscular blocking drugs, Bermejo, N., *et al.* 322–325
Complications, aneurysm, Cardiac function in aneurysmal subarachnoid haemorrhage, Moulay, N., *et al.*, (*ESA*) A.108
——, Helicopter transportation of patients with symptomatic aortic aneurysms, Fellbiter, P., *et al.*, (*ESA*) A.196
Complications, anti-cardiolipin antibody syndrome, Anaesthetic implications of the anti-cardiolipin antibody syndrome, Menon, G., *et al.* 587–590
Complications, aortic rupture, Diagnosis of aortic rupture by transesophageal echocardiography (TEE), Goarin, J. P., *et al.*, (*ESA*) A.193
Complications, arthritis, Differential effects of specific delta and kappa opioid antagonists on the bidirectionnal effect of naloxone in arthritic rats, Cattaneo, I., *et al.*, (*ESA*) A.114
Complications, arytenoid dislocation, Spontaneous reposition of a dislocated arytenoid cartilage, Gauss, A., *et al.* 591–592
Complications, asphyxia, Adult respiratory distress syndrome after attempted strangulation, Murphy, P. G., *et al.* 583–586
Complications, aspiration, How long should patients fast before surgery? Time for new guidelines, Strunin, L., (*E*) 1–3
——, Preoperative drinking and gastric contents, Levy, D. M., *et al.*, (*C*) 701–702
——, Preoperative drinking and gastric contents, Strunin, L., (*C*) 702
——, Preoperative drinking does not affect gastric contents, Phillips, S., *et al.* 6–9
Complications, atelectasis, Recruitment of atelectasis during general anaesthesia: a CT-study, Rothen, H. U., *et al.*, (*ESA*) A.53
Complications, backache, Long-term backache after extradural or general anaesthesia for manual removal of placenta: preliminary report, Vickers, R. J., *et al.* 214–215
——, Lumbovertebral syndrome after extradural blood patch, Seeberger, M. D., *et al.*, (*C*) 489
——, Lumbovertebral syndrome after extradural blood patch, Stride, P. C., (*C*) 489
Complications, barotrauma, Histology aspects of pulmonary barotrauma in critically ill patients with acute respiratory failure, Rouby, J. J., *et al.*, (*ESA*) A.181
Complications, Burkitt's lymphoma, Is Burkitt's lymphoma an etiology or a differential diagnosis of malignant hyperthermia? Lienhart, A., *et al.*, (*ESA*) A.93
Complications, burns, Electrode burns during local hyperthermia, Stott, D. G., *et al.*, 370–371
Complications, coagulopathy, The haemostatic response to surgery and trauma, Murphy, W. G., *et al.* 205–213
Complications, colitis, Measurement of sigmoid intramural pH during orthotopic liver transplantation, Auroy, Y., *et al.*, (*ESA*) A.76
Complications, death, A national database for intensive care medicine in Sweden, Karling, M., (*ESA*) A.8

——, Death certification, Baskett, P. J. F., (*C*) 112
——, Death certification, Skinner, A. C., (*C*) 112
——, Editorial II—the National Confidential Enquiry into Perioperative Deaths, Lunn, J. N., *et al.*, (*C*) 382
——, Mortality in ITU patients receiving neuromuscular blocking drugs, Hunter, J. M., *et al.*, (*C*) 238–239
Complications, diabetes, Muscular paralysis and ventilatory failure caused by hyperkalaemia, Freeman, S. J., *et al.* 226–227
Complications, dural puncture, A continuous subdural block, Collier, C. B., *et al.* 462–465
——, Lumbovertebral syndrome after extradural blood patch, Seeberger, M. D., *et al.*, (*C*) 489
——, Lumbovertebral syndrome after extradural blood patch, Stride, P. C., (*C*) 489
——, Subdural catheterization and cord damage, Collier, C. B., (*C*) 384
——, Subdural catheterization and cord damage, McMenemin, I., (*C*) 384
Complications, embolism, Inhibition of increase of blood thromboxane concentration by acetylsalicylic acid after release of tourniquet in lower extremity operations, Ojanen, R., *et al.*, (*ESA*) A.94
——, Possible venous air embolism with a new water jet dissector, Smith, J. A. S. 466–467
——, Reassessment of bronchoalveolar lavage in the diagnosis of post traumatic pulmonary fat embolism, Mimoz, O., *et al.*, (*ESA*) A.180
——, Systemic gas embolism in pulmonary contusion diagnosed by transesophageal echocardiography, Saada, M., *et al.*, (*ESA*) A.194
Complications, endocardial endothelium damage, Endocardial endothelium modulates *in vivo* left ventricular performance, De Hert, S. G., *et al.*, (*ESA*) A.47
Complications, extradural abscess, Delayed presentation of an extradural abscess in a patient with alcohol abuse, Nordström, O., *et al.* 368–369
——, Extradural abscess after central nerve block, Wildsmith, J. A. W., (*E*) 387–388
——, Extradural abscess in the postpartum period, Kitching, A. J., *et al.*, (*C*) 703
——, Extradural abscess in the postpartum period, Ngan Kee, W. D., (*C*) 704
——, Extradural abscess in the postpartum period, Vasdev, G. M. S., *et al.*, (*C*) 703–704
——, Lumbovertebral syndrome after extradural blood patch, Seeberger, M. D., *et al.*, (*C*) 489
——, Lumbovertebral syndrome after extradural blood patch, Stride, P. C., (*C*) 489
——, Spinal extradural abscess: pursuit of vigilance, Bromage, P. R. 471–473
Complications, haemolysis, Does etomidate cause haemolysis? Doenicke, A., *et al.*, (*C*) 491
——, Does etomidate cause haemolysis? Wertz, E., (*C*) 490–491
Complications, haemorrhage, Cardiac function in aneurysmal subarachnoid haemorrhage, Moulay, N., *et al.*, (*ESA*) A.108
Complications, head injury, Jugular bulb metabolic monitoring during hyperventilation in severe head trauma patients, De Deyne, C., *et al.*, (*ESA*) A.106
——, Sufentanil increases intracranial pressure in patients with head trauma, Albanese, J., *et al.*, (*ESA*) A.107
Complications, headache, Best Quincke point needle for Caesarean section, Lyons, G., (*ESA*) A.174
——, Epidural blood patch for treatment of postdural puncture headache, Rosenberg, P. H., *et al.*, (*ESA*) A.129
——, Headache—new needles and spinal anaesthesia for C. section, Thormann, F., *et al.*, (*ESA*) A.173
——, Incidence of post dural puncture headache in young adults by the use of the Sprötte needle: 300 patients, Descraques, C., *et al.*, (*ESA*) A.127
——, Lumbovertebral syndrome after extradural blood patch, Seeberger, M. D., *et al.*, (*C*) 489
——, Lumbovertebral syndrome after extradural blood patch, Stride, P. C., (*C*) 489
——, Nine years of clinical experience with 29 gauge spinal needles, Dittmann, M., *et al.*, (*ESA*) A.126
——, Postdural puncture headaches are not related to the duration of spinal catheter placement, Liu, N., *et al.*, (*ESA*) A.128
——, Visualization of extradural blood patch for post lumbar puncture headache by magnetic resonance imaging, Griffiths, A. G., *et al.* 223–225
Complications, hyperkalaemia, Muscular paralysis and ventilatory failure caused by hyperkalaemia, Freeman, S. J., *et al.* 226–227
Complications, hypertension, Is the vasoconstrictive effect of cyclosporine mediated by endothelin in kidney transplantation? Mouquet, C., *et al.*, (*ESA*) A.84
——, The pressor response to venous cannulation: attenuation by prior infiltration with local anaesthetic, Langham, B. T., *et al.* 519–521
Complications, hyperthermia, Exercise and malignant hyperthermia: family investigations, Kozak Ribbens, G., *et al.*, (*ESA*) A.92
——, Is Burkitt's lymphoma an etiology or a differential diagnosis of malignant hyperthermia? Lienhart, A., *et al.*, (*ESA*) A.93
Complications, hypoglycaemia, Neonatal glycemia: does the maternal i.v. fluid regimen during labor make a difference? Menigaux, C., *et al.*, (*ESA*) A.175
Complications, hypotension, Adrenaline-induced hypotension in neurosurgery, Phillips, S., *et al.* 687–688
——, Influence of chronic angiotensin converting enzyme inhibition on systolic pressure variation during anesthetic induction, Puybasset, L., *et al.*, (*ESA*) A.39
——, Ketamine does not prevent hypotension caused by induction of anaesthesia with propofol in elderly patients, Blockmans, D., *et al.*, (*ESA*) A.40
——, Mechanisms of ECG changes during Caesarean section (CS)—a hypothesis, Svanström, M., *et al.*, (*ESA*) A.177
——, Prevention and treatment of hypotension during central neural block, McCrae, A. F., *et al.* 672–680
——, Spinal anesthesia for C section: addition of phenylephrine to ephedrine for prevention of maternal hypotension, Thirion, A.-V., *et al.*, (*ESA*) A.172
Complications, hypothermia, An investigation into the effect of passive and active cutaneous warming devices on intraoperative body temperature in elderly patients, Bennet, J., *et al.*, (*ESA*) A.73
——, Effect of premedication with nifedipine on intraoperative hypothermia, Vassilieff, N., *et al.*, (*ESA*) A.71
——, Evaluation of the efficacy of forced-air warmer (Bair Hugger) during spinal surgery in children, Murat, I., *et al.*, (*ESA*) A.165
——, Preoperative skin-surface warming reduces intraoperative hypothermia, Camus, Y., *et al.*, (*ESA*) A.72
Complications, hypovolaemia, A comparison between various hemodynamic parameters reflecting preload during graded hemorrhage in ventilated dogs, Preisman, S., *et al.*, (*ESA*) A.51
——, Determinants of systolic pressure variation in patients ventilated after vascular surgery, Beaussier, M., *et al.*, (*ESA*) A.37
——, Effects of plasma volume substitution on right ventricle volumes and function using Elohes® and Plasmion®, Lepage, J. Y., *et al.*, (*ESA*) A.35
——, Evaluation of cardiac function in ICU: right heart catheterization *vs* transesophageal echocardiography. Preliminary results, Vivien, B., *et al.*, (*ESA*) A.183
——, Hypertonic solutions in acute massive haemorrhage, Brimacombe, J., *et al.*, (*C*) 705
——, Hypertonic solutions in acute massive haemorrhage, Park, G. R., (*C*) 706
——, Influence of chronic angiotensin converting enzyme inhibition on systolic pressure variation during anesthetic induction, Puybasset, L., *et al.*, (*ESA*) A.39
——, The systolic pressure variation predicts response to volume loading in patients ventilated after aortic surgery, Coriat, P., *et al.*, (*ESA*) A.38
Complications, hypoxaemia, Continuous monitoring of Sp_{O_2} during total intravenous anaesthesia with ketamine and spontaneous ventilation, Joly, L.-M., *et al.*, (*ESA*) A.58
——, Hypoxic events after general anaesthesia in the recovery room, Degasperi, D., *et al.*, (*ESA*) A.59
——, Influence of anaesthesia on post-operative hypoxaemia, Georgiou, L., *et al.*, (*ESA*) A.60
——, Postoperative hypoxaemia: comparison of epidural and patient controlled analgesia, Spencer, A., *et al.*, (*ESA*) A.207
Complications, infections, External ventricular CSF drains infections, Mahé, V., *et al.*, (*ESA*) A.109
Complications, intubation endobronchial, Continuous spirometry for detection of double-lumen endobronchial tube displacement, Bardoczky, G. I., *et al.* 499–502
Complications, intubation tracheal, Mathematical analysis of the upper respiratory tract from an anthropometric study, Janvier, G., *et al.* 186–191
Complications, laryngotracheo-oesophageal cleft, A bifurcated endobronchial tube in the management of laryngotracheo-oesophageal cleft repair, Ahmad, R., *et al.* 696–698
Complications, liver disease, Hepatotoxicity of volatile anaesthetics, Elliott, R. H., *et al.* 339–348

Complications, mucosal damage, Pressure exerted by the laryngeal mask airway cuff upon the pharyngeal mucosa, Marjot, R. 25–29

Complications, myocardial infarction, Effects of nitrous oxide (N_2O) on systemic haemodynamics, regional left ventricular (LV) function and incidence of myocardial ischaemia (MI) in vascular surgical patients with coronary artery disease (CAD), Hohner, P., *et al.*, (*ESA*) A.41

Complications, myolysis, Exercise and malignant hyperthermia: family investigations, Kozak Ribbens, G., *et al.*, (*ESA*) A.92

Complications, neurological, Explaining risk to patients, Chambers, W. A., (*C*) 381–382

——, Explaining risk to patients, Potter, F. A., (*C*) 381

——, Flumazenil facilitates intraoperative arousal in scoliosis surgery, Koscielniak-Nielsen, Z. J., *et al.*, (*ESA*) A.157

——, Spinal extradural abscess: pursuit of vigilance, Bromage, P. R. 471–473

——, Subdural catheterization and cord damage, Collier, C. B., (*C*) 384

——, Subdural catheterization and cord damage, McMenemin, I., (*C*) 384

Complications, obesity, Perioperative management of the obese patient, Shenkman, Z., *et al.* 349–359

——, The respiratory compliance in normal and obese subjects during anaesthesia, Mulazzi, D., *et al.*, (*ESA*) A.54

Complications, obstructive airways disease, Effects of PEEP on dynamic hyperinflation in patients with airflow limitation, Tan, I. K. S., *et al.* 267–272

Complications, osteoarthrosis, Diaphragmatic function after bupivacaine cervical extradural analgesia for chronic pain therapy, Nyström, E., *et al.*, (*ESA*) A.65

Complications, paralysis, Muscular paralysis and ventilatory failure caused by hyperkalaemia, Freeman, S. J., *et al.* 226–227

——, Spinal extradural abscess: pursuit of vigilance, Bromage, P. R. 471–473

Complications, phaeochromocytoma, Use of transoesophageal echocardiography to manage beta-adrenoceptor block and assess left ventricular function in a patient with phaeochromocytoma, Ryan, T., *et al.* 101–103

Complications, poisoning, The management of acute poisoning, Collee, G. G., *et al.* 562–573

Complications, porphyria, Xylometazoline and porphyria, Platt, N. D., (*C*) 491

Complications, pulmonary, Reassessment of bronchoalveolar lavage in the diagnosis of post traumatic pulmonary fat embolism, Mimoz, O., *et al.*, (*ESA*) A.180

——, Septic shock: effect of a goal-directed therapy on oxygen metabolism and serum cytokine levels, Martin, C., *et al.*, (*ESA*) A.189

Complications, pulmonary oedema, neurogenic, Adult respiratory distress syndrome after attempted strangulation, Murphy, P. G., *et al.* 583–586

Complications, regurgitation, Preoperative drinking does not affect gastric contents, Phillips, S., *et al.* 6–9

——, Regurgitation and the laryngeal mask airway, Brimacombe, J., *et al.*, (*C*) 381

——, Regurgitation and the laryngeal mask airway, Vanner, R. G., (*C*) 380–381

Complications, renal, Outcome for patients in intensive care with acute renal failure requiring dialysis, Ejlersen, E., *et al.*, (*ESA*) A.7

——, Prevention of acute tubular necrosis by volume loading in kidney transplantation, Mouquet, C., *et al.*, (*ESA*) A.82

——, Volume loading and hormonal factors in the prevention of acute tubular necrosis in kidney transplantation, Mouquet, C., *et al.*, (*ESA*) A.83

Complications, respiratory, Continuous spirometry: an aid in the intraoperative respiratory monitoring—case reports, Bardoczky, G., *et al.*, (*ESA*) A.55

Complications, respiratory depression, A comparison of midazolam and midazolam plus fentanyl for colonoscopy, Dupont, H., *et al.*, (*ESA*) A.9

Complications, septicaemia, Comparison of thoracic electrical bioimpedance and thermodilution for the measurement of cardiac index in patients with severe sepsis, Young, J. D., *et al.* 58–62

——, Comparison of two therapeutic strategies of septic shock, Martin, C., *et al.*, (*ESA*) A.190

——, Influence of N-acetylcysteine on O_2 consumption and gastric intramucosal pH in septic patients, Spies, C., *et al.*, (*ESA*) A.186

——, Influence of norepinephrine therapy on the oxygen supply and lactate extraction rate of the liver in the septic pig, Schäfer, R., *et al.*, (*ESA*) A.184

——, Molecular mediators and post-bacteraemic phase, Martínez Urionabarrenetxea, K., *et al.*, (*ESA*) A.187

——, Non invasive monitoring of CO_2 in patients with septic shock, Bodin, L., *et al.*, (*ESA*) A.191

——, Septic shock: effect of a goal-directed therapy on oxygen metabolism and serum cytokine levels, Martin, C., *et al.*, (*ESA*) A.189

——, The effect of dobutamine and norepinephrine on global and splanchnic O_2 consumption, Meier-Hellmann, A., *et al.*, (*ESA*) A.185

Complications, shivering, Effect of radiant heat on the metabolic cost of postoperative shivering, Sharkey, A., *et al.* 449–450

——, Fentanyl, as pethidine, inhibits post anaesthesia shivering, Alfonsi, P., *et al.*, (*ESA*) A.74

Complications, sinusitis, Incidence of bacterial maxillary sinusitis in critically ill patients with radiologic maxillary sinusitis, Bodin, L., *et al.*, (*ESA*) A.179

Complications, smokers, Effect of stopping smoking on upper airway reflexes, Erskine, R. J., *et al.*, (*ARS*) 478P

Complications, spontaneous excitatory movements, Spontaneous excitatory movements during recovery from propofol anaesthesia in an infant: EEG evaluation, Borgeat, A., *et al.* 459–461

Complications, stenosis, Dipyridamole-TEE and 24 h Holter-ECG as preoperative screening tests for coronary artery disease in patients with abdominal aortic aneurysm, Östman, M., *et al.*, (*ESA*) A.22

——, Does routine preoperative coronary angiography modify outcome after aortic surgery? Gosgnach, M., *et al.*, (*ESA*) A.6

——, Evaluation of haemodynamic indices of myocardial ischaemia in patients with coronary artery disease (CAD), Hohner, P., *et al.*, (*ESA*) A.23

——, Indications for coronary revascularisation in vascular surgical patients, Gosgnach, M., *et al.*, (*ESA*) A.5

——, Pulmonary and systemic vascular effects of isoproterenol, nitroglycerin and prostaglandin E1 early after cardiac operations in patients with pulmonary hypertension, Alvarez, J., *et al.*, (*ESA*) A.27

——, Sensitivity and specificity of mechanical and electrocardiographic myocardial ischaemia (MI) monitoring techniques, Hohner, P., *et al.*, (*ESA*) A.26

——, The use of the CUSUM plot for determination of myocardial ischaemia threshold during atrial pacing in patients with coronary artery disease, Reiz, S., *et al.*, (*ESA*) A.24

Complications, systemic lupus erythematosus, Anaesthetic implications of the anti-cardiolipin antibody syndrome, Menon, G., *et al.* 587–590

Complications, thrombosis, Anaesthetic implications of the anti-cardiolipin antibody syndrome, Menon, G., *et al.* 587–590

——, Aprotinin does not decrease surgical bleeding and could promote arterial thrombosis in the pig: a prospective randomized, blind, study, Samama, C. M., *et al.*, (*ESA*) A.100

——, Inhibition of increase of blood thromboxane concentration by acetylsalicylic acid after release of tourniquet in lower extremity operations, Ojanen, R., *et al.*, (*ESA*) A.94

Complications, trauma, Diagnosis of aortic rupture by transesophageal echocardiography (TEE), Goarin, J. P., *et al.*, (*ESA*) A.193

——, Evaluation of systematic TEE in patients suspected of blunt chest trauma, Catoire, P., *et al.*, (*ESA*) A.192

——, Jugular bulb metabolic monitoring during hyperventilation in severe head trauma patients, De Deyne, C., *et al.*, (*ESA*) A.106

——, Reassessment of bronchoalveolar lavage in the diagnosis of post traumatic pulmonary fat embolism, Mimoz, O., *et al.*, (*ESA*) A.180

——, Sufentanil increases intracranial pressure in patients with head trauma, Albanese, J., *et al.*, (*ESA*) A.107

——, Systemic gas embolism in pulmonary contusion diagnosed by transesophageal echocardiography, Saada, M., *et al.*, (*ESA*) A.194

——, The haemostatic response to surgery and trauma, Murphy, W. G., *et al.* 205–213

Complications, ultrasound, Endocardial endothelium modulates *in vivo* left ventricular performance, De Hert, S. G., *et al.*, (*ESA*) A.47

Computers, A national database for intensive care medicine in Sweden, Karling, M., (*ESA*) A.8

Conduction Blockade for Postoperative Analgesia: Mechanisms and Management, McClure, J. H., *et al.*, (editors), (*R*) 239

Cough, Postoperative laryngeal function assessed by tussometry, Lamb, J. M., *et al.*, (*ARS*) 478–479P

Diabetes, Muscular paralysis and ventilatory failure caused by hyperkalaemia, Freeman, S. J., *et al.* 226–227
Dimethylthiourea, Anaesthetic properties of dimethylthiourea, Koblin, D. D., *et al.* 456–458
Dog, A comparison between various hemodynamic parameters reflecting preload during graded hemorrhage in ventilated dogs, Preisman, S., *et al.*, (*ESA*) A.51
——, Acute haemodynamic effect of sodium bicarbonate in canine respiratory or metabolic acidosis, Nishikawa, T. 196–200
——, Does exogenous dopamine reverse cardiovascular depression induced by isoflurane during thoracic epidural blockade? Raner, C., *et al.*, (*ESA*) A.49
——, Endocardial endothelium modulates *in vivo* left ventricular performance, De Hert, S. G., *et al.*, (*ESA*) A.47
——, Lemakalim reverses ventricular conduction impairment induced by a large dose of bupivacaine in anesthetized dogs, de La Coussaye, J. E., *et al.*, (*ESA*) A.121
——, Pharmacokinetics of propofol administered by infusion in dogs undergoing surgery, Nolan, A., *et al.* 546–551
Donors, organ transplantation, Effects of desmopressin (DDAVP) supplementation in brain dead organ donors (BDOD) on early recipient renal function, Guesde, R., *et al.*, (*ESA*) A.79
——, Fiberoptic bronchoscopy in brain dead organ donors, Riou, B., *et al.*, (*ESA*) A.80
Drug delivery, Blended anaesthesia in pediatric major surgery: top-up *vs* epidural continuous infusion, Savoia, G., *et al.*, (*ESA*) A.159
——, Tetanic fade during recovery from vecuronium block: comparison of systemic and isolated forearm administration, Campkin, N. T. A., *et al.* 581–582
——, Treatment of cancer pain with morphine (MO)—A double blind study of extradural (ED) *versus* intramuscular (im) routes of administration, Nath, S., *et al.*, (*ESA*) A.211
Drug delivery, bolus, Influence of cardiac output, injection time and injection volume on the initial mixing of drugs with venous blood after i.v. bolus administration to sheep, Upton, R. N., *et al.* 333–338
——, Prediction of infusion rate of vecuronium to maintain steady state using the bolus test dose technique, Morgan, R. J., *et al.*, (*ARS*) 481P
Drug delivery, computerized, Closed-loop feedback controlled administration of alfentanil during alfentanil–nitrous oxide anaesthesia, Schwilden, H., *et al.* 389–393
——, Comparison of midazolam with propofol for sedation in outpatient bronchoscopy, Crawford, M., *et al.* 419–422
——, Computer-controlled syringe pump improves safety of pharmacokinetic models, Duranteau, R., *et al.*, (*ESA*) A.148
——, Determination of a pharmacokinetic model for propofol induction of anaesthesia, Viviand, X., *et al.*, (*ESA*) A.150
——, Target-controlled intravenous sedation with propofol, Mergaert, C., *et al.*, (*ESA*) A.149
Drug delivery, infusion, Prediction of infusion rate of vecuronium to maintain steady state using the bolus test dose technique, Morgan, R. J., *et al.*, (*ARS*) 481P
Drug delivery, injection speed, Comparison of infusion rates of three i.v. anaesthetic agents for induction in elderly patients, Berthoud, M. C., *et al.* 423–427
——, Different rates of injection of propofol, Goodman, N. W., (*C*) 383
——, Different rates of injection of propofol, Peacock, J. E., *et al.*, (*C*) 383–384
——, Influence of cardiac output, injection time and injection volume on the initial mixing of drugs with venous blood after i.v. bolus administration to sheep, Upton, R. N., *et al.* 333–338
Drug delivery, nasal, Comparison of nasal cannulae with face mask for oxygen administration to postoperative patients, Nolan, K. M., *et al.* 440–442
——, Intranasal fentanyl for breakthrough cancer pain or incident pain, Striebel, W. H., *et al.*, (*ESA*) A.210
——, Intranasal fentanyl for postoperative pain management in an unselected population, Striebel, W. H., *et al.*, (*ESA*) A.209
——, Pharmacokinetics of intranasal fentanyl, Striebel, H. W., *et al.*, (*ESA*) A.208
——, Plasma concentrations of midazolam after i.v., nasal or rectal administration in children, Malinovsky, J.-M., *et al.* 617–620
Drug delivery, oral, Dose dependent effects of oral medication with midazolam, Biro, P., *et al.*, (*ESA*) A.156
——, High dose oral morphine in cancer pain management, Radbruch, L., *et al.*, (*ESA*) A.212
Drug delivery, rectal, Plasma concentrations of midazolam after i.v., nasal or rectal administration in children, Malinovsky, J.-M., *et al.* 617–620
Drug delivery, transdermal, Pharmacokinetic behaviour of transdermal fentanyl, Van Bastelaere, M., *et al.*, (*ESA*) A.146

Education, junior staff, Nine years of clinical experience with 29 gauge spinal needles, Dittmann, M., *et al.*, (*ESA*) A.126
Electrical systems, burns, Electrode burns during local hyperthermia, Stott, D. G., *et al.* 370–371
Electrical Trauma: the Pathophysiology, Manifestations and Clinical Management, Lee, R. C., *et al.*, (editors), (*R*) 601
Embolism, air, Possible venous air embolism with a new water jet dissector, Smith, J. A. S. 466–467
——, Systemic gas embolism in pulmonary contusion diagnosed by transesophageal echocardiography, Saada, M., *et al.*, (*ESA*) A.194
Embolism, fat, Reassessment of bronchoalveolar lavage in the diagnosis of post traumatic pulmonary fat embolism, Mimoz, O., *et al.*, (*ESA*) A.180
Enzymes, acetyl cholinesterase, Prejunctional action of neostigmine on mouse neuromuscular preparations, Braga, M. F. M., *et al.* 405–410
Enzymes, angiotensin converting, inhibition, Does captopril modify the arterial response to vasopressor substances? Le Pelley, E., *et al.*, (*ESA*) A.48
——, Influence of chronic angiotensin converting enzyme inhibition on systolic pressure variation during anesthetic induction, Puybasset, L., *et al.*, (*ESA*) A.39
Enzymes, cholinesterase, Pharmacokinetics of the isomers of mivacurium chloride in the healthy adult, Head-Rapson, A. G., *et al.*, (*ARS*) 487P
——, Prejunctional action of neostigmine on mouse neuromuscular preparations, Braga, M. F. M., *et al.* 405–410
Enzymes, creatine kinase, Cardiac function in aneurysmal subarachnoid haemorrhage, Moulay, N., *et al.*, (*ESA*) A.108
Enzymes, phosphodiesterase, inhibition, Haemodynamic changes produced by inhalation anaesthetics in the presence of phosphodiesterase inhibition, Molter, G., *et al.* 428–433
Equipment, airway, Comparison of the reinforced laryngeal mask airway and tracheal intubation for adenotonsillectomy, Williams, P. J., *et al.* 30–33
——, Cricoid pressure and the laryngeal mask airway, Blogg, C. E., *et al.*, (*C*) 596–597
——, Cricoid pressure and the laryngeal mask airway, Brimacombe, J., *et al.*, (*C*) 596
——, Cricoid pressure and the laryngeal mask airway, Heath, M. L., *et al.*, (*C*) 596
——, Extra inspiratory work of breathing imposed by cricothyrotomy devices, Ooi, R., *et al.* 17–21
——, Is correlation of arterial and end-tidal carbon dioxide pressure during inhalation anaesthesia better with laryngeal mask as compared to face mask? Ivens, D., *et al.*, (*ESA*) A.17
——, Pressure exerted by the laryngeal mask airway cuff upon the pharyngeal mucosa, Marjot, R. 25–29
——, Regurgitation and the laryngeal mask airway, Brimacombe, J., *et al.*, (*C*) 381
——, Regurgitation and the laryngeal mask airway, Vanner, R. G., (*C*) 380–381
——, Relationship between arterial $P\text{CO}_2$ (Pa_{CO_2}) and end tidal CO_2 (ETCO_2) recorded through a laryngeal mask (LMA) in children breathing spontaneously, Van Obbergh, L. J., *et al.*, (*ESA*) A.164
——, The airway decides the anaesthetic approach before tracheal intubation, Williamson, R., (*C*) 600
——, The laryngeal mask airway in paediatric practice, Wilson, I. G., (*E*) 124–125
——, The laryngeal mask and intraocular surgery, Ripart, J., *et al.*, (*C*) 704
——, Use of the laryngeal mask and face mask by inexperienced personnel, Tighe, S. Q. M., (*C*) 114–115
——, Use of the laryngeal mask and face mask by inexperienced personnel, Tolley, P., *et al.*, (*C*) 115
——, Use of the laryngeal mask and face mask by inexperienced personnel, Walker, M. B., *et al.*, (*C*) 114
——, Ventilation with halothane is less affected in children with laryngeal mask airway than with endotracheal tube, Reignier, J., *et al.*, (*ESA*) A.162
Equipment, blankets, Preoperative skin-surface warming reduces intraoperative hypothermia, Camus, Y., *et al.*, (*ESA*) A.72
Equipment, blankets reflective, An investigation into the effect of passive and active cutaneous warming devices on

intraoperative body temperature in elderly patients, Bennet, J., *et al.*, (*ESA*) A.73
Equipment, breathing systems, Accumulation of acetone in blood during long-term anaesthesia with closed systems, Strauß, J. M., *et al.* 363–364
——, Fractional utilization of fresh gas by breathing systems without carbon dioxide absorption, Beatty, P. C. W., *et al.*, (*C*) 707
——, Fractional utilization of fresh gas by breathing systems without carbon dioxide absorption, Ravishankar, M., *et al.*, (*C*) 706–707
——, Frequency of damaged coaxial breathing systems, Robinson, D. L., (*C*) 384
——, Fresh gas requirements of an enclosed afferent reservoir breathing system in anaesthetized, spontaneously breathing adults, Barrie, J. R., *et al.* 468–470
Equipment, calibration, Clinical evaluation of the calibration of noninvasive continuous blood pressure measurement devices by means of oscillometric blood pressure measurements, de Jong, J. R., *et al.*, (*ESA*) A.15
Equipment, cannulae intravascular, Extra inspiratory work of breathing imposed by cricothyrotomy devices, Ooi, R., *et al.* 17–21
Equipment, cannulae nasal, Comparison of nasal cannulae with face mask for oxygen administration to postoperative patients, Nolan, K. M., *et al.* 440–442
Equipment, catheters subarachnoid, Postdural puncture headaches are not related to the duration of spinal catheter placement, Liu, N., *et al.*, (*ESA*) A.128
Equipment, Cell Saver, Preoperative autotransfusion in emergency surgery for spine trauma, Riou, B., *et al.*, (*ESA*) A.102
Equipment, computers, Computer-controlled syringe pump improves safety of pharmacokinetic models, Duranteau, R., *et al.*, (*ESA*) A.148
——, Determination of a pharmacokinetic model for propofol induction of anaesthesia, Viviand, X., *et al.*, (*ESA*) A.150
——, Target-controlled intravenous sedation with propofol, Mergaert, C., *et al.*, (*ESA*) A.149
Equipment, cuffs endobronchial, Endobronchial cuff pressures, Cobley, M., *et al.* 576–578
Equipment, cuffs tracheal, Pressure exerted by the laryngeal mask airway cuff upon the pharyngeal mucosa, Marjot, R. 25–29
——, Tracheal tube cuff inflation as an aid to blind nasotracheal intubation, Van Elstraete, A. C., *et al.* 691–693
Equipment, Dinamap, Comparison of automatic oscillometric arterial pressure measurement with conventional auscultatory measurement in the labour ward, Hasan, M. A., *et al.* 141–144
Equipment, electrodes, Electrode burns during local hyperthermia, Stott, D. G., *et al.* 370–371
Equipment, gas analysers, Evaluation of the Rascal II monitor, Palayiwa, E., *et al.*, (*ARS*) 485P
Equipment, gas exchangers, i.v., IVOX, Skoyles, J., *et al.*, (*E*) 603–604
Equipment, heat exchangers, oesophageal, Clinical evaluation of the oesophageal heat exchanger in the prevention of perioperative hypothermia, Kulkarni, P., *et al.* 216–218
Equipment, heat-moisture exchangers, Bacterial retention properties of heat and moisture exchange filters, Fox, D., (*C*) 382
——, Bacterial retention properties of heat and moisture exchange filters, Lee, M. G., (*C*) 382
——, Preservation of humidity and heat of respiratory gases in patients with minute ventilation > 10 l/min, Martin, C., *et al.*, (*ESA*) A.20
Equipment, helicopters, Helicopter transportation of patients with symptomatic aortic aneurysms, Felleiter, P., *et al.*, (*ESA*) A.196
——, The part of rescue helicopters in large accidents and disasters, Wenker, O., (*ESA*) A.197
Equipment, humidifiers, Effectiveness of core warming on net transfer of body heat across the skin, Kulkarni, P., *et al.*, (*ESA*) A.70
——, Preservation of humidity and heat of respiratory gases in patients with minute ventilation > 10 l/min, Martin, C., *et al.*, (*ESA*) A.20
Equipment, infusion systems, Computer-controlled syringe pump improves safety of pharmacokinetic models, Duranteau, R., *et al.*, (*ESA*) A.148
——, Determination of a pharmacokinetic model for propofol induction of anaesthesia, Viviand, X., *et al.*, (*ESA*) A.150
——, Target-controlled intravenous sedation with propofol, Mergaert, C., *et al.*, (*ESA*) A.149
Equipment, masks anaesthesia, Comparison of nasal cannulae with face mask for oxygen administration to postoperative patients, Nolan, K. M., *et al.* 440–442
——, Comparison of the reinforced laryngeal mask airway and tracheal intubation for adenotonsillectomy, Williams, P. J., *et al.* 30–33
——, Cricoid pressure and the laryngeal mask airway, Blogg, C. E., *et al.*, (*C*) 596–597
——, Cricoid pressure and the laryngeal mask airway, Brimacombe, J., *et al.*, (*C*) 596
——, Cricoid pressure and the laryngeal mask airway, Heath, M. L., *et al.*, (*C*) 596
——, Is correlation of arterial and end-tidal carbon dioxide pressure during inhalation anaesthesia better with laryngeal mask as compared to face mask? Ivens, D., *et al.*, (*ESA*) A.17
——, Nitrous oxide administration via oxygen therapy devices, Goddard, J. M., (*C*) 238
——, Nitrous oxide administration via oxygen therapy devices, Joshi, P., *et al.*, (*C*) 238
——, Pressure exerted by the laryngeal mask airway cuff upon the pharyngeal mucosa, Marjot, R. 25–29
——, Regurgitation and the laryngeal mask airway, Brimacombe, J., *et al.*, (*C*) 381
——, Regurgitation and the laryngeal mask airway, Vanner, R. G., (*C*) 380–381
——, Routine preoxygenation: how long before mask anaesthesia? Head-Rapson, A. G., *et al.*, (*ARS*) 488P
——, The laryngeal mask airway in paediatric practice, Wilson, I. G., (*E*) 124–125
——, The laryngeal mask and intraocular surgery, Ripart, J., *et al.*, (*C*) 704
——, Use of the laryngeal mask and face mask by inexperienced personnel, Tighe, S. Q. M., (*C*) 114–115
——, Use of the laryngeal mask and face mask by inexperienced personnel, Tolley, P., *et al.*, (*C*) 115
——, Use of the laryngeal mask and face mask by inexperienced personnel, Walker, M. B., *et al.*, (*C*) 114
Equipment, masks surgical, Face masks and spinal anaesthesia, O'Kelly, S. W., *et al.*, (*C*) 239
——, Face masks and spinal anaesthesia, Wildsmith, J. A. W., (*C*) 239
Equipment, needles, Best Quincke point needle for Caesarean section, Lyons, G., (*ESA*) A.174
——, "Concorde nose" in Whitacre spinal needles, McLeod, G. A., *et al.*, (*C*) 593
——, Headache—new needles and spinal anaesthesia for C. section, Thormann, F., *et al.*, (*ESA*) A.173
——, Incidence of post dural puncture headache in young adults by the use of the Sprôtte needle: 300 patients, Descraques, C., *et al.*, (*ESA*) A.127
——, Metal particle generation caused by the combined spinal–extradural technique, Hargreaves, J., (*C*) 706
——, Nine years of clinical experience with 29 gauge spinal needles, Dittmann, M., *et al.*, (*ESA*) A.126
——, Peripheral nerve damage and regional anaesthesia, Baranowski, A. P., *et al.*, (*C*) 593–594
——, Peripheral nerve damage and regional anaesthesia, Gentili, M. E., *et al.*, (*C*) 594
——, Peripheral nerve damage and regional anaesthesia, Rice, A. S. C., *et al.*, (*C*) 594
Equipment, retractors, Abdominal wall retraction may decrease anaesthesiological risks of laparoscopic cholecystectomy, Vereczkey, Z., *et al.*, (*ESA*) A.64
Equipment, sensors, Influence of posture on the respiratory mechanics during anesthesia, Engelman, E., *et al.*, (*ESA*) A.56
Equipment, temperature conservation, Effect of radiant heat on the metabolic cost of postoperative shivering, Sharkey, A., *et al.* 449–450
Equipment, tourniquets, Inhibition of increase of blood thromboxane concentration by acetylsalicylic acid after release of tourniquet in lower extremity operations, Ojanen, R., *et al.*, (*ESA*) A.94
Equipment, tubes double-lumen, A bifurcated endobronchial tube in the management of laryngotracheo-oesophageal cleft repair, Ahmad, R., *et al.* 696–698
——, Continuous spirometry for detection of double-lumen endobronchial tube displacement, Bardoczky, G. I., *et al.* 499–502
——, Double-lumen tubes, Vaughan, R. S., (*E*) 497–498
——, Endobronchial cuff pressures, Cobley, M., *et al.* 576–578
Equipment, tubes endobronchial, A bifurcated endobronchial tube in the management of laryngotracheo-oesophageal cleft repair, Ahmad, R., *et al.* 696–698
——, Continuous spirometry for detection of double-lumen endobronchial tube displacement, Bardoczky, G. I., *et al.* 499–502
——, Double-lumen tubes, Vaughan, R. S., (*E*) 497–498
——, Endobronchial cuff pressures, Cobley, M., *et al.* 576–578

Equipment, tubes tracheal, Evidence for dynamic phenomena in residual tracheal tube biofilm, Inglis, T. J. J. 22–24

——, Mathematical analysis of the upper respiratory tract from an anthropometric study, Janvier, G., *et al.* 186–191

Equipment, tubes tracheal, biofilm, Penetration of an aerosol, produced by film atomization, through the carinal bifurcation, Inglis, T. J. J., *et al.* 527–531

Equipment, tubes tracheostomy, Extra inspiratory work of breathing imposed by cricothyrotomy devices, Ooi, R., *et al.* 17–21

Equipment, ventilators, Comparison of portable emergency ventilators using a lung model, Attebo, L., *et al.* 372–377

——, Comparison of pressure support ventilation provided by two ICU ventilators, Kalfon, P., *et al.*, (*ESA*) A.182

Equipment, warming devices, An investigation into the effect of passive and active cutaneous warming devices on intraoperative body temperature in elderly patients, Bennet, J., *et al.*, (*ESA*) A.73

——, Effectiveness of core warming on net transfer of body heat across the skin, Kulkarni, P., *et al.*, (*ESA*) A.70

——, Evaluation of a forced-air warmer (Bair-Hugger) in maintaining body temperature in infants during cleft palate surgery, Murat, I., *et al.*, (*ESA*) A.166

——, Evaluation of the efficacy of forced-air warmer (Bair Hugger) during spinal surgery in children, Murat, I., *et al.*, (*ESA*) A.165

——, Preoperative skin-surface warming reduces intraoperative hypothermia, Camus, Y., *et al.*, (*ESA*) A.72

Equipment, water jet dissector, Possible venous air embolism with a new water jet dissector, Smith, J. A. S. 466–467

Errata, A physiological model for the distribution of injected agents, with special reference to pethidine, Davis, N. R., *et al.* 711

——, Extra inspiratory work of breathing imposed by cricothyrotomy devices, Ooi, R., *et al.* 494

——, Haemodynamic effects of periodic ventilation: abolition with supplementary oxygen, Reeder, M. K., *et al.* 119

——, *MCQ for the Higher Examination in Clinical Pharmacology*, McCarthy, G., *et al.*, (*R*) 241

——, Postoperative hypoxaemia after major abdominal vascular surgery, Reeder, M. K., *et al.* 119

——, Postoperative myocardial ischaemia: temporal association with nocturnal hypoxaemia, Reeder, M. K., *et al.* 119

——, Pressure exerted by the laryngeal mask airway cuff upon the pharyngeal mucosa, Marjot, R. 711

Essay Plans for Anaesthesia Exams, Michel, M. Z., *et al.*, (*R*) 709

Ethics, Explaining risk to patients, Chambers, W. A., (*C*) 381–382

——, Explaining risk to patients, Potter, F. A., (*C*) 381

——, Spinal extradural abscess: pursuit of vigilance, Bromage, P. R. 471–473

Eye, cataract, Pharmacokinetics and effects of i.m. alfentanil as premedication for outpatient cataract surgery, Ali-Melkkilä, T., *et al.*, (*ESA*) A.145

Eye, orbicularis oculi, Monitoring the onset of neuromuscular blockade at the orbicularis oculi can predict good intubating conditions when using $2 \times ED_{95}$ of atracurium, Debaene, B., *et al.*, (*ESA*) A.142

Fatigue, Laparoscopic *vs* open cholecystectomy, Jakeways, M. S. R., *et al.*, (*C*) 597

Fetus, Incremental spinal anaesthesia for elective Caesarean section: maternal and fetal haemodynamic effects, Robson, S. C., *et al.* 634–638

——, Intermittent *vs* continuous extradural infusion of bupivacaine during labour, Eddleston, J. M., (*C*) 490

——, Intermittent *vs* continuous extradural infusion of bupivacaine during labour, Laishley, R. S., (*C*) 490

Fluid balance, Effects of desmopressin (DDAVP) supplementation in brain dead organ donors (BDOD) on early recipient renal function, Guesde, R., *et al.*, (*ESA*) A.79

——, Ultrasound measurement of muscle thickness in the estimation of fat free mass, Watt, T., *et al.*, (*ARS*) 477P

Fluids, irrigating, Glycine and its metabolites during and after intrauterine YAG laser surgery, Van Boven, M. J., *et al.*, (*ESA*) A.87

Fluids, i.v., Neonatal glycemia: does the maternal i.v. fluid regimen during labor make a difference? Menigaux, C., *et al.*, (*ESA*) A.175

Fluids, oral, How long should patients fast before surgery? Time for new guidelines, Strunin, L., (*E*) 1–3

——, Preoperative drinking and gastric contents, Levy, D. M., *et al.*, (*C*) 701–702

——, Preoperative drinking and gastric contents, Mather, C., (*C*) 702

——, Preoperative drinking and gastric contents, Phillips, S., *et al.*, (*C*) 702–703

——, Preoperative drinking and gastric contents, Read, M. S., *et al.*, (*C*) 701

——, Preoperative drinking and gastric contents, Strunin, L., (*C*) 702

——, Preoperative drinking does not affect gastric contents, Phillips, S., *et al.* 6–9

Forensic medicine, Midazolam premedication: a forensic approach to pharmacokinetics and amnesia, Motsch, J., *et al.*, (*ESA*) A.155

Formulations, bupivacaine, Epidural administration of liposomal bupivacaine for the management of postsurgical pain, Boogaerts, J., *et al.*, (*ESA*) A.200

Formulations, diazepam, Effects of diazepam additives on the mononuclear phagocytic system, Catalá, J. C., *et al.*, (*ESA*) A.89

Formulations, diluents, Benzodiazepines and their solvents influence neutrophil granulocyte function, Weiss, M., *et al.* 317–321

——, Does etomidate cause haemolysis? Doenicke, A., *et al.*, (*C*) 491

——, Does etomidate cause haemolysis? Wertz, E., (*C*) 490–491

——, Effects of diazepam additives on the mononuclear phagocytic system, Catalá, J. C., *et al.*, (*ESA*) A.89

Formulations, emulsifiers, Propofol decreases random and chemotactic stimulated locomotion of human neutrophils *in vitro*, Jensen, A. G., *et al.* 99–100

Formulations, etomidate, Adrenocortical function: a clinical comparison of Etomidat-Lipuro® and Hypnomidate®, Wiebalck, A., *et al.*, (*ESA*) A.90

——, Quality of induction: a clinical comparison of Etomidat-Lipuro® and Hypnomidate®, Wiebalck, A., *et al.*, (*ESA*) A.154

Formulations, liposomes, Epidural administration of liposomal bupivacaine for the management of postsurgical pain, Boogaerts, J., *et al.*, (*ESA*) A.200

——, Motor blockade and absence of local nerve toxicity induced by liposomal bupivacaine injected into the axillary brachial plexus of rabbits, Legros, F. J., *et al.*, (*ESA*) A.122

Formulations, pH, Slow-release effect of pH-adjusted bupivacaine: pharmacokinetic demonstration, Benhamou, D., *et al.*, (*ESA*) A.120

Gases non-anaesthetic, Asymmetry of uptake and washout of inert gases—lessons learnt in an anaesthetic department, Flook, V., (*ARS*) 487–488P

——, Effect on lung volumes of oxygen concentration when breathing is restricted, Baker, A. B., *et al.* 259–266

——, Hyperbaric decompression bubble formation—building on the Mapleson model of gas dynamics, Flook, V., *et al.*, (*ARS*) 474–475P

Gastrointestinal tract, gastroscopy, Studies of gastric content: comparison of two methods, Søreide, E., *et al.* 360–362

Gastrointestinal tract, intestine, Local *versus* neurogenic vasodilator effects of desflurane and isoflurane in the small intestine, Sundeman, H., *et al.*, (*ESA*) A.50

Gastrointestinal tract, lower oesophageal sphincter, Regurgitation and the laryngeal mask airway, Brimacombe, J., *et al.*, (*C*) 381

——, Regurgitation and the laryngeal mask airway, Vanner, R. G., (*C*) 380–381

Gastrointestinal tract, mucosal perfusion, Gastric mucosal perfusion is better preserved during cardiac surgery when isoflurane rather than enflurane or propofol is used to maintain anaesthesia, Mythen, M., *et al.*, (*ESA*) A.29

——, Influence of N-acetylcysteine on O_2 consumption and gastric intramucosal pH in septic patients, Spies, C., *et al.*, (*ESA*) A.186

——, Measurement of sigmoid intramural pH during orthotopic liver transplantation, Auroy, Y., *et al.*, (*ESA*) A.76

Gastrointestinal tract, pH, How long should patients fast before surgery? Time for new guidelines, Strunin, L., (*E*) 1–3

——, Preoperative drinking and gastric contents, Levy, D. M., *et al.*, (*C*) 701–702

——, Preoperative drinking and gastric contents, Mather, C., (*C*) 702

——, Preoperative drinking and gastric contents, Read, M. S., *et al.*, (*C*) 701

——, Preoperative drinking does not affect gastric contents, Phillips, S., *et al.* 6–9

——, Studies of gastric content: comparison of two methods, Søreide, E., *et al.* 360–362

Gastrointestinal tract, volume, How long should patients fast before surgery? Time for new guidelines, Strunin, L., *(E)* 1–3
——, Preoperative drinking and gastric contents, Levy, D. M., *et al.*, *(C)* 701–702
——, Preoperative drinking and gastric contents, Mather, C., *(C)* 702
——, Preoperative drinking and gastric contents, Read, M. S., *et al.*, *(C)* 701
——, Preoperative drinking does not affect gastric contents, Phillips, S., *et al.* 6–9
——, Studies of gastric content: comparison of two methods, Søreide, E., *et al.* 360–362
Genetic factors, Clonal variation in response to enflurane anaesthesia with *Daphnia magna*, Myles, A. P., *et al.*, *(ARS)* 476–477P
Genetic factors, hyperthermia, Combined caffeine–halothane test for malignant hyperthermia, Ellis, F. R., *et al.*, *(C)* 598
——, Combined caffeine–halothane test for malignant hyperthermia, Nelson, T. E., *(C)* 597–598
——, Comparison of *in vitro* contracture testing with ryanodine, halothane and caffeine in malignant hyperthermia and other neuromuscular disorders, Hopkins, P. M., *et al.* 397–401
——, Exercise and malignant hyperthermia: family investigations, Kozak Ribbens, G., *et al.*, *(ESA)* A.92
——, Genetic linkage analysis of chromosome 19 markers in malignant hyperthermia, Ball, S. P., *et al.* 70–75

Handbook of Percutaneous Central Venous Catheterisation, 2nd Edn, Rosen, M., *et al.*, (editors), *(R)* 601
Heart, arrhythmia, bradycardia, Cardiovascular effects of a pancuronium–vecuronium mixture, Doyle, M., *et al.*, *(ARS)* 486–487P
Heart, arrhythmia, fibrillation, Pre- and intraoperative prevention by β-blockers, propranolol and esmolol, of ischaemia-induced ventricular fibrillation, Freysz, M., *et al.*, *(ESA)* A.46
——, Use of lignocaine in ventricular defibrillation? Baskett, P. J. F., *(C)* 380
——, Use of lignocaine in ventricular defibrillation? Quiney, N. F., *et al.*, *(C)* 380
Heart, blood flow, myocardial, Effects of hypertonic saline on coronary blood flow and myocardial performance of a blood-perfused, isolated rabbit heart, Delayance, S., *et al.*, *(ESA)* A.45
Heart, cardiac massage, The choice of ECM rate could improve the neuroprotection during CPR, Iannuzzi, E., *et al.*, *(ESA)* A.195
Heart, cardiac output, Alternating right to left ventricular ejection; the case of occult cardiac tamponade, Skourtis, C., *et al.*, *(ESA)* A.36
——, Cardiac output (CO) measurement: comparison of esophageal Doppler (ED) *vs* thermodilution (TD), Lefrant, J. Y., *et al.*, *(ESA)* A.18
——, Cardiac output determined from pulmonary gas exchange, Österlund, B., *et al.*, *(ESA)* A.19
——, Changes in haemodynamic variables with thiopentone, methohexitone, propofol and etomidate, Price, M., *(C)* 116
——, Changes in haemodynamic variables with thiopentone, methohexitone, propofol and etomidate, Williams, E. L., *(C)* 115
——, Comparison of thoracic electrical bioimpedance and thermodilution for the measurement of cardiac index in patients with severe sepsis, Young, J. D., *et al.* 58–62
——, Determinants of systolic pressure variation in patients ventilated after vascular surgery, Beaussier, M., *et al.*, *(ESA)* A.37
——, Evaluation in intensive care of the fraction area change obtained by automatic border detection, Liu, N., *et al.*, *(ESA)* A.25
——, Influence of cardiac output, injection time and injection volume on the initial mixing of drugs with venous blood after i.v. bolus administration to sheep, Upton, R. N., *et al.* 333–338
——, Statistical assessment of two methods of clinical measurement, Berridge, J. C., *(C)* 595
——, Statistical assessment of two methods of clinical measurement, Runcie, C. J., *(C)* 595
——, The choice of ECM rate could improve the neuroprotection during CPR, Iannuzzi, E., *et al.*, *(ESA)* A.195
Heart, cardiopulmonary bypass, Acute preoperative plasmapheresis during cardiac surgery, Armellin, G., *et al.*, *(ESA)* A.104
——, Comparison of dobutamine with enoximone following open heart surgery in small children, Innes, P., *et al.*, *(ESA)* A.167
——, High dose aprotinin *versus* desmo-pressin acetate treatment in cardiac surgery, Hidalgo, F., *et al.*, *(ESA)* A.99
——, The relationship between cardiopulmonary bypass related immunologic effects and complement, thromboxane and leucocyte parameters, Durak, P., *et al.*, *(ESA)* A.96
Heart, catheterization, Evaluation of cardiac function in ICU: right heart catheterization *vs* transesophageal echocardiography. Preliminary results, Vivien, B., *et al.*, *(ESA)* A.183
Heart, conduction, Lemakalim reverses ventricular conduction impairment induced by a large dose of bupivacaine in anesthetized dogs, de La Coussaye, J. E., *et al.*, *(ESA)* A.121
Heart, congenital defects, Extracorporeal membrane oxygenation for postoperative cardiac support in newborn infants: first clinical data, Marcassa, A., *et al.*, *(ESA)* A.168
——, Metabolic effects of corrective surgery in infants and children with congenital heart defects, Puhakka, K., *et al.* 149–153
Heart, coronary artery bypass, Core–peripheral temperature difference in early *vs* later extubation after coronary artery surgery, Knapik, P., *et al.*, *(ESA)* A.69
——, Does propofol supplemented anaesthesia affect neurophysiological outcome following cardiopulmonary bypass? Phillips, A. S., *et al.*, *(ARS)* 484P
——, Does routine preoperative coronary angiography modify outcome after aortic surgery? Gosgnach, M., *et al.*, *(ESA)* A.6
——, Early postperfusion assessment of gas exchange and postoperative extubation outcome following coronary artery surgery, Knapik, P., *et al.*, *(ESA)* A.61
——, Echocardiographic study of the induction with a low-dose of sufentanil for coronary artery surgery, Bromberg, N., *et al.*, *(ESA)* A.28
——, Effects of lorazepam on oxygen saturation before cardiac surgery, Pollock, J. S. S., *et al.* 219–220
——, Gastric mucosal perfusion is better preserved during cardiac surgery when isoflurane rather than enflurane or propofol is used to maintain anaesthesia, Mythen, M., *et al.*, *(ESA)* A.29
——, Indications for coronary revascularisation in vascular surgical patients, Gosgnach, M., *et al.*, *(ESA)* A.5
——, Preoperative clonidine improves postoperative renal function in CABG patients, Kulka, P. J., *et al.*, *(ESA)* A.143
Heart, coronary occlusion, Effects of nitrous oxide (N_2O) on systemic haemodynamics, regional left ventricular (LV) function and incidence of myocardial ischaemia (MI) in vascular surgical patients with coronary artery disease (CAD), Hohner, P., *et al.*, *(ESA)* A.41
Heart, dobutamine, Comparison of dobutamine with enoximone following open heart surgery in small children, Innes, P., *et al.*, *(ESA)* A.167
Heart, enoximone, Comparison of dobutamine with enoximone following open heart surgery in small children, Innes, P., *et al.*, *(ESA)* A.167
——, Haemodynamic changes produced by inhalation anaesthetics in the presence of phosphodiesterase inhibition, Molter, G., *et al.* 428–433
Heart, esmolol, Pre- and intraoperative prevention by β-blockers, propranolol and esmolol, of ischaemia-induced ventricular fibrillation, Freysz, M., *et al.*, *(ESA)* A.46
——, Use of esmolol in the postbypass management of hypertrophic obstructive cardiomyopathy, Ooi, L. G., *et al.* 104–106
——, Use of transoesophageal echocardiography to manage beta-adrenoceptor block and assess left ventricular function in a patient with phaeochromocytoma, Ryan, T., *et al.* 101–103
Heart, heart rate, Effects of surgical stimulation on autonomic reflex function: assessment by changes in heart rate variability, Latson, T. W., *et al.* 301–305
——, Pre- and intraoperative prevention by β-blockers, propranolol and esmolol, of ischaemia-induced ventricular fibrillation, Freysz, M., *et al.*, *(ESA)* A.46
Heart, inotropism, Haemodynamic changes produced by inhalation anaesthetics in the presence of phosphodiesterase inhibition, Molter, G., *et al.* 428–433
Heart, ischaemia, Dipyridamole-TEE and 24 h Holter-ECG as preoperative screening tests for coronary artery disease in patients with abdominal aortic aneurysm, Östman, M., *et al.*, *(ESA)* A.22
——, Effects of nitrous oxide (N_2O) on systemic haemodynamics, regional left ventricular (LV) function

and incidence of myocardial ischaemia (MI) in vascular surgical patients with coronary artery disease (CAD), Hohner, P., *et al.*, (*ESA*) A.41
——, Epidural clonidine and myocardial ischaemia after abdominal aortic surgery, Fulgencio, J. P., *et al.*, (*ESA*) A.42
——, Evaluation of haemodynamic indices of myocardial ischaemia in patients with coronary artery disease (CAD), Hohner, P., *et al.*, (*ESA*) A.23
——, Functional recovery after 24 h preservation of rabbit hearts in University Wisconsin solution, Fellahi, J. L., *et al.*, (*ESA*) A.44
——, Influence of cervicothoracic epidural anaesthesia (C-TEA) on left ventricular (LV) contractility—an experimental study in pigs with autonomous blockade, Reiz, S., *et al.*, (*ESA*) A.52
——, Influence of positive pressure ventilation on myocardial ischaemia after abdominal aortic aneurysm repair, McCoy, D., *et al.*, (*ESA*) A.43
——, Pre- and intraoperative prevention by β-blockers, propranolol and esmolol, of ischaemia-induced ventricular fibrillation, Freysz, M., *et al.*, (*ESA*) A.46
——, Sensitivity and specificity of mechanical and electrocardiographic myocardial ischaemia (MI) monitoring techniques, Hohner, P., *et al.*, (*ESA*) A.26
——, The use of the CUSUM plot for determination of myocardial ischaemia threshold during atrial pacing in patients with coronary artery disease, Reiz, S., *et al.*, (*ESA*) A.24
——, Tolerance of preoperative transesophageal echocardiography in patients scheduled for aortic surgery, Gosgnach, M., *et al.*, (*ESA*) A.21
Heart, isolated preparation, Effects of hypertonic saline on coronary blood flow and myocardial performance of a blood-perfused, isolated rabbit heart, Delayance, S., *et al.*, (*ESA*) A.45
——, Functional recovery after 24 h preservation of rabbit hearts in University Wisconsin solution, Fellahi, J. L., *et al.*, (*ESA*) A.44
Heart, isoprenaline, Pulmonary and systemic vascular effects of isoproterenol, nitroglycerin and prostaglandin E1 early after cardiac operations in patients with pulmonary hypertension, Alvarez, J., *et al.*, (*ESA*) A.27
Heart, myocardial function, Cardiac function in aneurysmal subarachnoid haemorrhage, Moulay, N., *et al.*, (*ESA*) A.108
——, Effects of hypertonic saline on coronary blood flow and myocardial performance of a blood-perfused, isolated rabbit heart, Delayance, S., *et al.*, (*ESA*) A.45
——, Evaluation of cardiac function in ICU: right heart catheterization *vs* transesophageal echocardiography. Preliminary results, Vivien, B., *et al.*, (*ESA*) A.183
——, Evaluation of haemodynamic indices of myocardial ischaemia in patients with coronary artery disease (CAD), Hohner, P., *et al.*, (*ESA*) A.23
——, Functional recovery after 24 h preservation of rabbit hearts in University Wisconsin solution, Fellahi, J. L., *et al.*, (*ESA*) A.44
——, I.v. bolus administration of subconvulsive doses of lignocaine to conscious sheep: relationships between myocardial pharmacokinetics and pharmacodynamics, Huang, Y. F., *et al.* 556–561
——, Propofol/fentanyl-anesthesia in patients with highly depressed cardiac function, Rauch, H., *et al.*, (*ESA*) A.30
——, Tolerance of preoperative transesophageal echocardiography in patients scheduled for aortic surgery, Gosgnach, M., *et al.*, (*ESA*) A.21
——, Transoesophageal echocardiographic assessment of haemodynamic function during laparoscopic cholecystectomy, Cunningham, A. J., *et al.* 621–625
Heart, myopathy, Use of esmolol in the postbypass management of hypertrophic obstructive cardiomyopathy, Ooi, L. G., *et al.* 104–106
Heart, nitroglycerin, Pulmonary and systemic vascular effects of isoproterenol, nitroglycerin and prostaglandin E1 early after cardiac operations in patients with pulmonary hypertension, Alvarez, J., *et al.*, (*ESA*) A.27
Heart, pacemakers artificial, EEG-monitoring during defibrillator-implantation: effects of repetitive cerebral ischemia on electric brain activity, Spies, C., *et al.*, (*ESA*) A.110
Heart, preservation, Functional recovery after 24 h preservation of rabbit hearts in University Wisconsin solution, Fellahi, J. L., *et al.*, (*ESA*) A.44
Heart, propranolol, Pre- and intraoperative prevention by β-blockers, propranolol and esmolol, of ischaemia-induced ventricular fibrillation, Freysz, M., *et al.*, (*ESA*) A.46
Heart, resuscitation, Death certification, Baskett, P. J. F., (*C*) 112
——, Death certification, Skinner, A. C., (*C*) 112
——, The choice of ECM rate could improve the neuroprotection during CPR, Iannuzzi, E., *et al.*, (*ESA*) A.195
——, Use of lignocaine in ventricular defibrillation? Baskett, P. J. F., (*C*) 380
——, Use of lignocaine in ventricular defibrillation? Quiney, N. F., *et al.*, (*C*) 380
——, Use of the laryngeal mask and face mask by inexperienced personnel, Tighe, S. Q. M., (*C*) 114–115
——, Use of the laryngeal mask and face mask by inexperienced personnel, Tolley, P., *et al.*, (*C*) 115
——, Use of the laryngeal mask and face mask by inexperienced personnel, Walker, M. B., *et al.*, (*C*) 114
Heart, tamponade, Alternating right to left ventricular ejection; the case of occult cardiac tamponade, Skourtis, C., *et al.*, (*ESA*) A.36
Heart, transplantation, Functional recovery after 24 h preservation of rabbit hearts in University Wisconsin solution, Fellahi, J. L., *et al.*, (*ESA*) A.44
Heart, vascular pressures, A comparison between various hemodynamic parameters reflecting preload during graded hemorrhage in ventilated dogs, Preisman, S., *et al.*, (*ESA*) A.51
——, Alternating right to left ventricular ejection; the case of occult cardiac tamponade, Skourtis, C., *et al.*, (*ESA*) A.36
——, Changes in haemodynamic variables with thiopentone, methohexitone, propofol and etomidate, Price, M., (*C*) 116
——, Changes in haemodynamic variables with thiopentone, methohexitone, propofol and etomidate, Williams, E. L., (*C*) 115
——, Determinants of systolic pressure variation in patients ventilated after vascular surgery, Beaussier, M., *et al.*, (*ESA*) A.37
——, Evaluation of haemodynamic indices of myocardial ischaemia in patients with coronary artery disease (CAD), Hohner, P., *et al.*, (*ESA*) A.23
——, Haemodynamic and metabolic consequences of aortic occlusion during abdominal aortic surgery, Whalley, D. G., *et al.* 96–98
——, Influence of chronic angiotensin converting enzyme inhibition on systolic pressure variation during anesthetic induction, Puybasset, L., *et al.*, (*ESA*) A.39
——, Shunt flow and caval pressure gradient during veno-venous bypass in human orthotopic liver transplantation, Scherer, R. U., *et al.* 689–690
——, The systolic pressure variation predicts response to volume loading in patients ventilated after aortic surgery, Coriat, P., *et al.*, (*ESA*) A.38
Heart, ventricles, Effects of nitrous oxide (N_2O) on systemic haemodynamics, regional left ventricular (LV) function and incidence of myocardial ischaemia (MI) in vascular surgical patients with coronary artery disease (CAD), Hohner, P., *et al.*, (*ESA*) A.41
——, Effects of plasma volume substitution on right ventricle volumes and function using Elohes® and Plasmion®, Lepage, J. Y., *et al.*, (*ESA*) A.35
——, Endocardial endothelium modulates *in vivo* left ventricular performance, De Hert, S. G., *et al.*, (*ESA*) A.47
——, Influence of cervicothoracic epidural anaesthesia (C-TEA) on left ventricular (LV) contractility—an experimental study in pigs with autonomous blockade, Reiz, S., *et al.*, (*ESA*) A.52
——, Influence of chronic angiotensin converting enzyme inhibition on systolic pressure variation during anesthetic induction, Puybasset, L., *et al.*, (*ESA*) A.39
——, The systolic pressure variation predicts response to volume loading in patients ventilated after aortic surgery, Coriat, P., *et al.*, (*ESA*) A.38
——, Use of transoesophageal echocardiography to manage beta-adrenoceptor block and assess left ventricular function in a patient with phaeochromocytoma, Ryan, T., *et al.* 101–103
Histamine, Anq 9040: effect of twice the ED_{95} dose, Munday, I. T., *et al.*, (*ARS*) 480P
——, Platelet serotonin is a mediator potentially involved in anaphylactic reaction to neuromuscular blocking drugs, Bermejo, N., *et al.* 322–325
Histamine, antihistamines, The combined prophylactic administration of H1 and H2 receptor blockers in the prevention of protamine related haemodynamic effects and the relation between antihistaminics-leucocytes and

pulmonary vascular resistance, Durak, P., *et al.*, (*ESA*) A.95

History, diethyl ether, John Henry Hill Lewellin: The first etherist in Glasgow, Macdonald, A. G. 228–234

History, Lewellin, John Henry Hill, John Henry Hill Lewellin: The first etherist in Glasgow, Macdonald, A. G. 228–234

Hormones, adrenal, Adrenocortical function: a clinical comparison of Etomidat-Lipuro® and Hypnomidate®, Wiebalck, A., *et al.*, (*ESA*) A.90

Hormones, adrenocorticotrophic, Adrenocortical function: a clinical comparison of Etomidat-Lipuro® and Hypnomidate®, Wiebalck, A., *et al.*, (*ESA*) A.90

Hormones, aldosterone, Modification of the renin–aldosterone axis during orthotopic liver transplantation, de los Ríos, J., *et al.*, (*ESA*) A.75

Hormones, antidiuretic, Anaesthesia affects plasma concentrations of vasopressin, von Willebrand factor and coagulation factor VIII in cardiac surgical patients, Kuitunen, A., *et al.* 173–180

——, Effects of desmopressin (DDAVP) supplementation in brain dead organ donors (BDOD) on early recipient renal function, Guesde, R., *et al.*, (*ESA*) A.79

——, High dose aprotinin *versus* desmo-pressin acetate treatment in cardiac surgery, Hidalgo, F., *et al.*, (*ESA*) A.99

Hormones, corticosteroid, Diaphragmatic function after bupivacaine cervical extradural analgesia for chronic pain therapy, Nyström, E., *et al.*, (*ESA*) A.65

Hormones, glucocorticoid, Effects of etomidate on the adrenocortical and metabolic adaptation of the neonate, Crozier, T. A., *et al.* 47–53

Hormones, growth, Effect of recombinant human growth hormone (HGH) on protein metabolism in surgical patients, Carli, F., *et al.*, (*ESA*) A.86

——, The role of recombinant growth factors in transfusion medicine, Goodnough, L. T. 80–86

Hormones, insulin, Effects of midazolam on insulin secretion from isolated rat pancreatic islets of Langerhans, Desborough, J. P., *et al.* 221–222

——, Isoflurane inhibits Ca^{2+}-induced insulin secretion from electrically permeabilised islets of Langerhans, Desborough, J. P., *et al.*, (*ESA*) A.91

Hormones, messenger, Effects of morphine and its metabolites on opiate receptor binding and cyclic adenosine-3′,5′-monophosphate (cAMP) formation in human neuroblastoma cells, Lambert, D. G., *et al.*, (*ARS*) 475–476P

——, Halothane enhances forskolin stimulated cyclic adenosine-3′,5′-monophosphate formation in human neuroblastoma cells, Hirst, R. A., *et al.*, (*ARS*) 486P

Hormones, progesterone, Adrenocortical function: a clinical comparison of Etomidat-Lipuro® and Hypnomidate®, Wiebalck, A., *et al.*, (*ESA*) A.90

Hormones, prostaglandins, Pulmonary and systemic vascular effects of isoproterenol, nitroglycerin and prostaglandin E1 early after cardiac operations in patients with pulmonary hypertension, Alvarez, J., *et al.*, (*ESA*) A.27

Hormones, renin, Adrenocortical function: a clinical comparison of Etomidat-Lipuro® and Hypnomidate®, Wiebalck, A., *et al.*, (*ESA*) A.90

——, Modification of the renin–aldosterone axis during orthotopic liver transplantation, de los Ríos, J., *et al.*, (*ESA*) A.75

Hyperalgesia and Allodynia, Willis, W., (editor), (*R*) 385

Hyperbaria, pressure reversal, Asymmetry of uptake and washout of inert gases—lessons learnt in an anaesthetic department, Flook, V., (*ARS*) 487–488P

——, Hyperbaric decompression bubble formation—building on the Mapleson model of gas dynamics, Flook, V., *et al.*, (*ARS*) 474–475P

Hyperhidrosis, Transthoracic endoscopic sympathectomy, Gilligan, S., *et al.*, (*C*) 491

——, Transthoracic endoscopic sympathectomy, Jedeiken, R., *et al.*, (*C*) 491–492

——, Transthoracic endoscopic sympathectomy, Plastow, S. E., *et al.*, (*C*) 492

Hyperthermia, diathermy, Electrode burns during local hyperthermia, Stott, D. G., *et al.* 370–371

Hypertrophic obstructive cardiomyopathy, Use of esmolol in the postbypass management of hypertrophic obstructive cardiomyopathy, Ooi, L. G., *et al.* 104–106

Hypnotics benzodiazepine, diazepam, Benzodiazepines and their solvents influence neutrophil granulocyte function, Weiss, M., *et al.* 317–321

——, Effect of oral diazepam on the sensitivity of upper airway reflexes, Murphy, P. J., *et al.* 131–134

——, Effects of diazepam additives on the mononuclear phagocytic system, Catalá, J. C., *et al.*, (*ESA*) A.89

——, Hepatic elimination of diazepam: interactions with albumin, desflurane and sevoflurane, Dale, O., *et al.* 454–455

Hypnotics benzodiazepine, flunitrazepam, Effects of midazolam and flunitrazepam on the release of dopamine from rat striatum measured by *in vivo* microdialysis, Takada, K., *et al.* 181–185

——, Metabolic effects of propofol and flunitrazepam given for sedation after aortic surgery, Moritz, F., *et al.* 451–453

Hypnotics benzodiazepine, lorazepam, Effects of lorazepam on oxygen saturation before cardiac surgery, Pollock, J. S. S., *et al.* 219–220

Hypnotics benzodiazepine, midazolam, A comparison of midazolam and midazolam plus fentanyl for colonoscopy, Dupont, H., *et al.*, (*ESA*) A.9

——, Benzodiazepines and their solvents influence neutrophil granulocyte function, Weiss, M., *et al.* 317–321

——, Comparison of midazolam with propofol for sedation in outpatient bronchoscopy, Crawford, M., *et al.* 419–422

——, Comparison of the sedative and amnesic effects of midazolam and propofol, Polster, M. R., *et al.* 612–616

——, Dexmedetomidine does not exercise its anesthetic action through GABA, Salonen, M., *et al.*, (*ESA*) A.113

——, Direct spinal effect of intrathecal and extradural midazolam on visceral noxious stimulation in rabbits, Crawford, M. E., *et al.* 642–646

——, Dose dependent effects of oral medication with midazolam, Biro, P., *et al.*, (*ESA*) A.156

——, Effects of midazolam and flunitrazepam on the release of dopamine from rat striatum measured by *in vivo* microdialysis, Takada, K., *et al.* 181–185

——, Effects of midazolam on insulin secretion from isolated rat pancreatic islets of Langerhans, Desborough, J. P., *et al.* 221–222

——, Midazolam–alfentanil: an anaesthetic? An investigation using the isolated forearm technique, Russell, I. F. 42–46

——, Midazolam premedication: a forensic approach to pharmacokinetics and amnesia, Motsch, J., *et al.*, (*ESA*) A.155

——, Midazolam prevents ketamine-induced stimulation of cerebral metabolism, Åkeson, J., *et al.*, (*ESA*) A.111

——, Pharmacokinetics of flumazenil and midazolam, Jones, R. D. M., *et al.* 286–292

——, Plasma concentrations of midazolam after i.v., nasal or rectal administration in children, Malinovsky, J.-M., *et al.* 617–620

——, Prolonged (> 1 week) sedation with midazolam in ICU patients: efficacy, safety and pharmacokinetics, Heytens, L., *et al.*, (*ESA*) A.178

Hypnotics butyrophenone, droperidol, Addition of droperidol to patient-controlled analgesia: effect on nausea and vomiting, Williams, O. A., *et al.*, (*ARS*) 479P

Hypothermia, Clinical evaluation of the oesophageal heat exchanger in the prevention of perioperative hypothermia, Kulkarni, P., *et al.* 216–218

——, Effect of radiant heat on the metabolic cost of postoperative shivering, Sharkey, A., *et al.* 449–450

Hypoxaemia, Continuous monitoring of Sp_{O_2} during total intravenous anaesthesia with ketamine and spontaneous ventilation, Joly, L.-M., *et al.*, (*ESA*) A.58

——, Hypoxic events after general anaesthesia in the recovery room, Degasperi, D., *et al.*, (*ESA*) A.59

——, Influence of anaesthesia on post-operative hypoxaemia, Georgiou, L., *et al.*, (*ESA*) A.60

——, Postoperative hypoxaemia: comparison of epidural and patient controlled analgesia, Spencer, A., *et al.*, (*ESA*) A.207

Hypoxia, Hepatotoxicity of volatile anaesthetics, Elliott, R. H., *et al.* 339–348

Hypoxia, Metabolic Acidosis and the Circulation, Arieff, A. I., (editor), (*R*) 118

Immune response, Anaesthetic implications of the anti-cardiolipin antibody syndrome, Menon, G., *et al.* 587–590

——, Effect of propofol on neutrophil respiratory burst, Ogilvy, A. J., *et al.*, (*ARS*) 476P

——, Propofol decreases random and chemotactic stimulated locomotion of human neutrophils *in vitro*, Jensen, A. G., *et al.* 99–100

——, The relationship between cardiopulmonary bypass related immunologic effects and complement, thromboxane and leucocyte parameters, Durak, P., *et al.*, (*ESA*) A.96

Immune response, post-anaesthetic hepatitis, Halothane, metabolite-induced antibodies and hepatotoxicity, Kenna, J. G., *et al.*, (*ARS*) 484–485P

——, Hepatotoxicity of volatile anaesthetics, Elliott, R. H., *et al.* 339–348

Immune response, suppression, Effects of diazepam additives on the mononuclear phagocytic system, Catalá, J. C., *et al.*, (*ESA*) A.89

——, Is the vasoconstrictive effect of cyclosporine mediated by endothelin in kidney transplantation? Mouquet, C., *et al.*, (*ESA*) A.84

Induction, anaesthesia, Cardiovascular effects of i.v. induction in children: comparison between propofol and thiopentone, Aun, C. S. T., *et al.* 647–653

——, Echocardiographic study of the induction with a low-dose of sufentanil for coronary artery surgery, Bromberg, N., *et al.*, (*ESA*) A.28

——, Haemodynamic and catecholamine responses to induction of anaesthesia and tracheal intubation: comparison between propofol and thiopentone, Lindgren, L., *et al.* 306–310

——, Influence of chronic angiotensin converting enzyme inhibition on systolic pressure variation during anesthetic induction, Puybasset, L., *et al.*, (*ESA*) A.39

——, Ketamine does not prevent hypotension caused by induction of anaesthesia with propofol in elderly patients, Blockmans, D., *et al.*, (*ESA*) A.40

——, Preoxygenation and Sp_{O_2} after induction of anaesthesia with propofol and fentanyl, Rittoo, D. B., *et al.*, (*ARS*) 486P

Infants, Comparison of dobutamine with enoximone following open heart surgery in small children, Innes, P., *et al.*, (*ESA*) A.167

——, Effect of extradural analgesia on stress responses to abdominal surgery in infants, Wolf, A. R., *et al.* 654–660

——, Evaluation of a forced-air warmer (Bair-Hugger) in maintaining body temperature in infants during cleft palate surgery, Murat, I., *et al.*, (*ESA*) A.166

——, Metabolic effects of corrective surgery in infants and children with congenital heart defects, Puhakka, K., *et al.* 149–153

——, Pain relief for infants undergoing abdominal surgery: comparison of infusions of i.v. morphine and extradural bupivacaine, Wolf, A. R., *et al.* 10–16

——, The pharmacokinetics of rocuronium in pediatric patients: a pooled data analysis, Meistelman, C., *et al.*, (*ESA*) A.138

——, Use of thoracic epidural block for perioperative analgesia in children, Entress, A. H., *et al.*, (*ESA*) A.158

——, Use of ultrasound to evaluate internal jugular vein anatomy and to facilitate central venous cannulation in paediatric patients, Alderson, P. J., *et al.* 145–148

——, Ventilation with halothane is less affected in children with laryngeal mask airway than with endotracheal tube, Reignier, J., *et al.*, (*ESA*) A.162

——, Volume replacement with hydroxyethyl starch solution in children, Boldt, J., *et al.* 661–665

Infection, bacterial, Bacterial retention properties of heat and moisture exchange filters, Fox, D., (*C*) 382

——, Bacterial retention properties of heat and moisture exchange filters, Lee, M. G., (*C*) 382

——, Evidence for dynamic phenomena in residual tracheal tube biofilm, Inglis, T. J. J. 22–24

——, Extradural abscess in the postpartum period, Ngan Kee, W. D., (*C*) 704

——, Extradural abscess in the postpartum period, Vasdev, G. M. S., *et al.*, (*C*) 703–704

——, Face masks and spinal anaesthesia, O'Kelly, S. W., *et al.*, (*C*) 239

——, Face masks and spinal anaesthesia, Wildsmith, J. A. W., (*C*) 239

——, Incidence of bacterial maxillary sinusitis in critically ill patients with radiologic maxillary sinusitis, Bodin, L., *et al.*, (*ESA*) A.179

——, Molecular mediators and cardiac surgery, Pérez Arancón, J. L., *et al.*, (*ESA*) A.188

——, Molecular mediators and post-bacteraemic phase, Martínez Urionabarrenetxea, K., *et al.*, (*ESA*) A.187

Infection, central nervous system, External ventricular CSF drains infections, Mahé, V., *et al.*, (*ESA*) A.109

Infection, control, Face masks and spinal anaesthesia, O'Kelly, S. W., *et al.*, (*C*) 239

——, Face masks and spinal anaesthesia, Wildsmith, J. A. W., (*C*) 239

Infection, nosocomial, Evidence for dynamic phenomena in residual tracheal tube biofilm, Inglis, T. J. J. 22–24

——, External ventricular CSF drains infections, Mahé, V., *et al.*, (*ESA*) A.109

——, Extradural abscess in the postpartum period, Ngan Kee, W. D., (*C*) 704

——, Extradural abscess in the postpartum period, Vasdev, G. M. S., *et al.*, (*C*) 703–704

——, Face masks and spinal anaesthesia, O'Kelly, S. W., *et al.*, (*C*) 239

——, Face masks and spinal anaesthesia, Wildsmith, J. A. W., (*C*) 239

——, Incidence of bacterial maxillary sinusitis in critically ill patients with radiologic maxillary sinusitis, Bodin, L., *et al.*, (*ESA*) A.179

——, Penetration of an aerosol, produced by film atomization, through the carinal bifurcation, Inglis, T. J. J., *et al.* 527–531

Infection, tetanus, Prolonged use of isoflurane in a patient with tetanus, Stevens, J. J. W. M., *et al.* 107–109

Intensive care, Cardiac output (CO) measurement: comparison of esophageal Doppler (ED) *vs* thermodilution (TD), Lefrant, J. Y., *et al.*, (*ESA*) A.18

——, Comparison of portable emergency ventilators using a lung model, Attebo, L., *et al.* 372–377

——, Comparison of pressure support ventilation provided by two ICU ventilators, Kalfon, P., *et al.*, (*ESA*) A.182

——, Comparison of two therapeutic strategies of septic shock, Martin, C., *et al.*, (*ESA*) A.190

——, Continuous monitoring of the ventilatory mechanics during anaesthesia & intensive care, Py, C., *et al.*, (*ESA*) A.57

——, Evaluation in intensive care of the fraction area change obtained by automatic border detection, Liu, N., *et al.*, (*ESA*) A.25

——, Evaluation of cardiac function in ICU: right heart catheterization *vs* transesophageal echocardiography. Preliminary results, Vivien, B., *et al.*, (*ESA*) A.183

——, Histology aspects of pulmonary barotrauma in critically ill patients with acute respiratory failure, Rouby, J. J., *et al.*, (*ESA*) A.181

——, Influence of N-acetylcysteine on O_2 consumption and gastric intramucosal pH in septic patients, Spies, C., *et al.*, (*ESA*) A.186

——, Molecular mediators and cardiac surgery, Pérez Arancón, J. L., *et al.*, (*ESA*) A.188

——, Mortality in ITU patients receiving neuromuscular blocking drugs, Hunter, J. M., *et al.*, (*C*) 238–239

——, Non invasive monitoring of CO_2 in patients with septic shock, Bodin, L., *et al.*, (*ESA*) A.191

——, Outcome for patients in intensive care with acute renal failure requiring dialysis, Ejlersen, E., *et al.*, (*ESA*) A.7

——, Preservation of humidity and heat of respiratory gases in patients with minute ventilation > 10 l/min, Martin, C., *et al.*, (*ESA*) A.20

——, Septic shock: effect of a goal-directed therapy on oxygen metabolism and serum cytokine levels, Martin, C., *et al.*, (*ESA*) A.189

——, Technical aspects of jugular bulb oximetry, De Deyne, C., *et al.*, (*ESA*) A.16

——, The management of acute poisoning, Collee, G. G., *et al.* 562–573

Intensive care, alcohol withdrawal, Carbohydrate deficient transferrin: a new copredictor of alcoholism related postoperative complications? Heil, T., *et al.*, (*ESA*) A.88

Intensive care, audit, A national database for intensive care medicine in Sweden, Karling, M., (*ESA*) A.8

Intensive care, infections, Evidence for dynamic phenomena in residual tracheal tube biofilm, Inglis, T. J. J. 22–24

——, Incidence of bacterial maxillary sinusitis in critically ill patients with radiologic maxillary sinusitis, Bodin, L., *et al.*, (*ESA*) A.179

——, Molecular mediators and post-bacteraemic phase, Martínez Urionabarrenetxea, K., *et al.*, (*ESA*) A.187

Intensive care, sedation, Prolonged (> 1 week) sedation with midazolam in ICU patients: efficacy, safety and pharmacokinetics, Heytens, L., *et al.*, (*ESA*) A.178

Interactions (drug), Cardiovascular effects of a pancuronium–vecuronium mixture, Doyle, M., *et al.*, (*ARS*) 486–487P

——, Does nicardipine potentiate the neuromuscular block of atracurium? Bazin, J. E., *et al.*, (*ESA*) A.136

——, Efficacy of postoperative pain treatment regimens using both buprenorphine and papaveretum sequentially after abdominal hysterectomy, Green, D. W., *et al.* 626–630

——, Haemodynamic changes produced by inhalation anaesthetics in the presence of phosphodiesterase inhibition, Molter, G., *et al.* 428–433

——, Hepatic elimination of diazepam: interactions with albumin, desflurane and sevoflurane, Dale, O., *et al.* 454–455

——, Isoproterenol reverses the MAC decreasing effect of esmolol in rats, Perel, A., *et al.*, (*ESA*) A.117

——, Midazolam prevents ketamine-induced stimulation of cerebral metabolism, Åkeson, J., *et al.*, (*ESA*) A.111
——, Nitrous oxide-mediated activation of the EEG during isoflurane anaesthesia in patients, Yli-Hankala, A., *et al.* 54–57
——, Partial reversal of the effects of extradural clonidine by oral yohimbine in postoperative patients, Liu, N., *et al.* 515–518
——, Pipecuronium-induced prolongation of vecuronium neuromuscular block, Smith, I., *et al.* 446–448
——, Synergy and isoboles, Calvey, T. N., (*E*) 246–247
——, The effect of parenteral diclofenac and morphine on efficacy duration and height of blockade during continuous epidural bupivacaine 0.5%, Forbes, D., *et al.*, (*ESA*) A.125
Intubation endobronchial, A bifurcated endobronchial tube in the management of laryngotracheo-oesophageal cleft repair, Ahmad, R., *et al.* 696–698
——, Double-lumen tubes, Vaughan, R. S., (*E*) 497–498
——, Endobronchial cuff pressures, Cobley, M., *et al.* 576–578
Intubation endobronchial, complications, Continuous spirometry for detection of double-lumen endobronchial tube displacement, Bardoczky, G. I., *et al.* 499–502
Intubation nasotracheal, technique, Comparison of alfentanil with suxamethonium in facilitating nasotracheal intubation in day-case anaesthesia, Alcock, R., *et al.* 34–37
——, Tracheal tube cuff inflation as an aid to blind nasotracheal intubation, Van Elstraete, A. C., *et al.* 691–693
——, Use of alfentanil with propofol for nasotracheal intubation without neuromuscular block, Coghlan, S. F. E., *et al.* 89–91
Intubation tracheal, Comparison of the reinforced laryngeal mask airway and tracheal intubation for adenotonsillectomy, Williams, P. J., *et al.* 30–33
——, Monitoring the onset of neuromuscular blockade at the orbicularis oculi can predict good intubating conditions when using 2×ED_{95} of atracurium, Debaene, B., *et al.*, (*ESA*) A.142
——, Propofol and alfentanil or thiopentone and suxamethonium for tracheal intubation, Beck, G. N., *et al.*, (*ARS*) 483P
——, Propofol for tracheal intubation in paediatric outpatient anaesthesia, Montasser, A. M., (*ESA*) A.161
Intubation tracheal, complications, Spontaneous reposition of a dislocated arytenoid cartilage, Gauss, A., *et al.* 591–592
Intubation tracheal, difficult, A new clinical score to predict difficult intubation, Arné, J., *et al.*, (*ESA*) A.1
——, The airway decides the anaesthetic approach before tracheal intubation, Vaughan, R. S., *et al.*, (*C*) 600
——, The airway decides the anaesthetic approach before tracheal intubation, Williamson, R., (*C*) 600
Intubation tracheal, extubation, Core–peripheral temperature difference in early *vs* later extubation after coronary artery surgery, Knapik, P., *et al.*, (*ESA*) A.69
——, Early postperfusion assessment of gas exchange and postoperative extubation outcome following coronary artery surgery, Knapik, P., *et al.*, (*ESA*) A.61
Intubation tracheal, responses, Effect of esmolol *versus* lidocaine on intracranial pressure and haemodynamic responses to laryngoscopy and intubation, Samaha, T., *et al.*, (*ESA*) A.118
——, Haemodynamic and catecholamine responses to induction of anaesthesia and tracheal intubation: comparison between propofol and thiopentone, Lindgren, L., *et al.* 306–310
Intubation tracheal, technique, Cricoid pressure and the laryngeal mask airway, Blogg, C. E., *et al.*, (*C*) 596–597
——, Cricoid pressure and the laryngeal mask airway, Brimacombe, J., *et al.*, (*C*) 596
——, Cricoid pressure and the laryngeal mask airway, Heath, M. L., *et al.*, (*C*) 596
——, The airway decides the anaesthetic approach before tracheal intubation, Williamson, R., (*C*) 600
——, Tracheal intubation after induction of anaesthesia with propofol, alfentanil and i.v. lignocaine, Davidson, J. A. H., *et al.* 163–166
——, Veterinary use of "Xylocaine" spray, Taylor, P. M., (*C*) 113
Ions, calcium, Isoflurane inhibits Ca^{2+}-induced insulin secretion from electrically permeabilised islets of Langerhans, Desborough, J. P., *et al.*, (*ESA*) A.91
Ions, fluoride, Prolonged use of isoflurane in a patient with tetanus, Stevens, J. J. W. M., *et al.* 107–109
Ions, magnesium, Priming of atracurium with magnesium, Lampl, E., *et al.*, (*ESA*) A.139
Ions, sodium, Effects of hypertonic saline on coronary blood flow and myocardial performance of a blood-perfused, isolated rabbit heart, Delayance, S., *et al.*, (*ESA*) A.45
——, Modification of the renin–aldosterone axis during orthotopic liver transplantation, de los Ríos, J., *et al.*, (*ESA*) A.75

Key Topics in Anaesthesia, Craft, T. M., *et al.*, (editors), (*R*) 117
Kidney, blood flow, Renal blood flow and function relationship in recent renal transplantation in man, Jacob, L., *et al.*, (*ESA*) A.85
Kidney, failure, Is the vasoconstrictive effect of cyclosporine mediated by endothelin in kidney transplantation? Mouquet, C., *et al.*, (*ESA*) A.84
——, Morphine-6-glucuronide disposition in renal impairment, Hanna, M. H., *et al.* 511–514
——, Outcome for patients in intensive care with acute renal failure requiring dialysis, Ejlersen, E., *et al.*, (*ESA*) A.7
——, Pharmacokinetics of propofol and its conjugates after continuous infusion in normal and renal failure patients, Nathan, N., *et al.*, (*ESA*) A.151
——, Pharmacokinetics of rocuronium (Org 9426) in patients with and without impaired renal function, Cooper, R., *et al.*, (*ARS*) 482P
——, Prevention of acute tubular necrosis by volume loading in kidney transplantation, Mouquet, C., *et al.*, (*ESA*) A.82
——, Volume loading and hormonal factors in the prevention of acute tubular necrosis in kidney transplantation, Mouquet, C., *et al.*, (*ESA*) A.83
Kidney, function, Effects of desmopressin (DDAVP) supplementation in brain dead organ donors (BDOD) on early recipient renal function, Guesde, R., *et al.*, (*ESA*) A.79
——, Preoperative clonidine improves postoperative renal function in CABG patients, Kulka, P. J., *et al.*, (*ESA*) A.143
——, Prolonged use of isoflurane in a patient with tetanus, Stevens, J. J. W. M., *et al.* 107–109
——, Renal blood flow and function relationship in recent renal transplantation in man, Jacob, L., *et al.*, (*ESA*) A.85
Kidney, lithotripsy, Propofol anaesthesia with spontaneous breathing for extracorporeal shock wave lithotripsy, Pasch, T., *et al.*, (*ESA*) A.153
Kidney, transplantation, Effects of desmopressin (DDAVP) supplementation in brain dead organ donors (BDOD) on early recipient renal function, Guesde, R., *et al.*, (*ESA*) A.79
——, Is the vasoconstrictive effect of cyclosporine mediated by endothelin in kidney transplantation? Mouquet, C., *et al.*, (*ESA*) A.84
——, Morphine-6-glucuronide disposition in renal impairment, Hanna, M. H., *et al.* 511–514
——, Prevention of acute tubular necrosis by volume loading in kidney transplantation, Mouquet, C., *et al.*, (*ESA*) A.82
——, Renal blood flow and function relationship in recent renal transplantation in man, Jacob, L., *et al.*, (*ESA*) A.85
——, Total intravenous anaesthesia (TIVA) with propofol and alfentanil for renal transplantation, Kirvelä, M., *et al.*, (*ESA*) A.81
——, Volume loading and hormonal factors in the prevention of acute tubular necrosis in kidney transplantation, Mouquet, C., *et al.*, (*ESA*) A.83
Kidney, urine metabolites, Modification of the renin–aldosterone axis during orthotopic liver transplantation, de los Ríos, J., *et al.*, (*ESA*) A.75

Larynx, cricoid pressure, Cricoid pressure and the laryngeal mask airway, Blogg, C. E., *et al.*, (*C*) 596–597
——, Cricoid pressure and the laryngeal mask airway, Brimacombe, J., *et al.*, (*C*) 596
——, Cricoid pressure and the laryngeal mask airway, Heath, M. L., *et al.*, (*C*) 596
Larynx, damage, Day 0 or day 3 laryngoscopy after thyroidectomy? Lacoste, L., *et al.*, (*ESA*) A.67
——, Direct, indirect or flexible laryngoscopy after thyroidectomy? Lacoste, L., *et al.*, (*ESA*) A.66
——, Postoperative laryngeal function assessed by tussometry, Lamb, J. M., *et al.*, (*ARS*) 478–479P
Larynx, laryngoscopy, Day 0 or day 3 laryngoscopy after thyroidectomy? Lacoste, L., *et al.*, (*ESA*) A.67
——, Direct, indirect or flexible laryngoscopy after thyroidectomy? Lacoste, L., *et al.*, (*ESA*) A.66
——, Effect of esmolol *versus* lidocaine on intracranial pressure and haemodynamic responses to laryngoscopy and intubation, Samaha, T., *et al.*, (*ESA*) A.118

——, Laryngeal function as assessed by tussometry following topical anaesthesia, Mahajan, R. P., *et al.*, (*ESA*) A.68
Larynx, laryngoscopy fibreoptic, Direct, indirect or flexible laryngoscopy after thyroidectomy? Lacoste, L., *et al.*, (*ESA*) A.66
Larynx, vocal cords, Concentration–effect relationship at the vocal cords and the adductor pollicis following rocuronium administration, Plaud, B., *et al.*, (*ESA*) A.141
——, Laryngeal function as assessed by tussometry following topical anaesthesia, Mahajan, R. P., *et al.*, (*ESA*) A.68
Liver, blood flow, The effect of dobutamine and norepinephrine on global and splanchnic O_2 consumption, Meier-Hellmann, A., *et al.*, (*ESA*) A.185
Liver, cirrhosis, Modification of the renin–aldosterone axis during orthotopic liver transplantation, de los Ríos, J., *et al.*, (*ESA*) A.75
——, Oxygen consumption is dependent upon oxygen delivery in cirrhotics undergoing liver transplantation, Piccinni, P., *et al.*, (*ESA*) A.78
Liver, hepatotoxicity, Halothane, metabolite-induced antibodies and hepatotoxicity, Kenna, J. G., *et al.*, (*ARS*) 484–485P
——, Hepatotoxicity of volatile anaesthetics, Elliott, R. H., *et al.* 339–348
Liver, metabolism, Hepatic elimination of diazepam: interactions with albumin, desflurane and sevoflurane, Dale, O., *et al.* 454–455
——, Hepatotoxicity of volatile anaesthetics, Elliott, R. H., *et al.* 339–348
——, Influence of norepinephrine therapy on the oxygen supply and lactate extraction rate of the liver in the septic pig, Schäfer, R., *et al.*, (*ESA*) A.184
Liver, microsomes, Halothane, metabolite-induced antibodies and hepatotoxicity, Kenna, J. G., *et al.*, (*ARS*) 484–485P
Liver, oxygen consumption, The effect of dobutamine and norepinephrine on global and splanchnic O_2 consumption, Meier-Hellmann, A., *et al.*, (*ESA*) A.185
Liver, transplantation, Blood requirements reduction in orthotopic liver transplantation with aprotinin, Monedero, P., *et al.*, (*ESA*) A.98
——, Changes in blood lactate, total body oxygen delivery and consumption during liver transplantation, Carrera, J., *et al.*, (*ESA*) A.77
——, Measurement of sigmoid intramural pH during orthotopic liver transplantation, Auroy, Y., *et al.*, (*ESA*) A.76
——, Modification of the renin–aldosterone axis during orthotopic liver transplantation, de los Ríos, J., *et al.*, (*ESA*) A.75
——, Oxygen consumption is dependent upon oxygen delivery in cirrhotics undergoing liver transplantation, Piccinni, P., *et al.*, (*ESA*) A.78
——, Shunt flow and caval pressure gradient during veno–venous bypass in human orthotopic liver transplantation, Scherer, R. U., *et al.* 689–690
Lung, adult respiratory distress syndrome, Adult respiratory distress syndrome after attempted strangulation, Murphy, P. G., *et al.* 583–586
——, Surfactant and adult respiratory distress syndrome, Jacobson, W., *et al.* 522–526
Lung, atelectasis, Effect on lung volumes of oxygen concentration when breathing is restricted, Baker, A. B., *et al.* 259–266
——, Recruitment of atelectasis during general anaesthesia: a CT-study, Rothen, H. U., *et al.*, (*ESA*) A.53
Lung, compliance, Comparison of portable emergency ventilators using a lung model, Attebo, L., *et al.* 372–377
——, Influence of posture on the respiratory mechanics during anesthesia, Engelman, E., *et al.*, (*ESA*) A.56
——, The respiratory compliance in normal and obese subjects during anaesthesia, Mulazzi, D., *et al.*, (*ESA*) A.54
Lung, damage, Adult respiratory distress syndrome after attempted strangulation, Murphy, P. G., *et al.* 583–586
——, Histology aspects of pulmonary barotrauma in critically ill patients with acute respiratory failure, Rouby, J. J., *et al.*, (*ESA*) A.181
——, Systemic gas embolism in pulmonary contusion diagnosed by transesophageal echocardiography, Saada, M., *et al.*, (*ESA*) A.194
Lung, function, Fiberoptic bronchoscopy in brain dead organ donors, Riou, B., *et al.*, (*ESA*) A.80
——, Lung function after vecuronium pretreatment in elderly patients, Mahajan, R. P., *et al.*, (*ARS*) 482–483P
Lung, functional residual capacity, Effect of selective cell separation on respiratory function after aortic aneurysm surgery, McKavney, M., *et al.*, (*ARS*) 475P
——, Effect of three different surgical prone positions on lung volumes in healthy, awake volunteers, Hennessy, N., *et al.*, (*ARS*) 475P
——, Effect on lung volumes of oxygen concentration when breathing is restricted, Baker, A. B., *et al.* 259–266
Lung, gas exchange, Cardiac output determined from pulmonary gas exchange, Österlund, B., *et al.*, (*ESA*) A.19
——, Effect of selective cell separation on respiratory function after aortic aneurysm surgery, McKavney, M., *et al.*, (*ARS*) 475P
Lung, intravascular pressures, Pulmonary and systemic vascular effects of isoproterenol, nitroglycerin and prostaglandin E1 early after cardiac operations in patients with pulmonary hypertension, Alvarez, J., *et al.*, (*ESA*) A.27
Lung, lavage, Reassessment of bronchoalveolar lavage in the diagnosis of post traumatic pulmonary fat embolism, Mimoz, O., *et al.*, (*ESA*) A.180
Lung, model, Comparison of portable emergency ventilators using a lung model, Attebo, L., *et al.* 372–377
Lung, respiratory resistance, Comparison of portable emergency ventilators using a lung model, Attebo, L., *et al.* 372–377
Lung, surfactant, Surfactant and adult respiratory distress syndrome, Jacobson, W., *et al.* 522–526
Lung, tidal volume, Comparison of spontaneous sighs and manual inflations in anaesthetized patients breathing air and oxygen, Dow, A. C., *et al.*, (*ARS*) 474P
Lung, transplantation, Fiberoptic bronchoscopy in brain dead organ donors, Riou, B., *et al.*, (*ESA*) A.80
Lung, volume, Effect of selective cell separation on respiratory function after aortic aneurysm surgery, McKavney, M., *et al.*, (*ARS*) 475P
——, Effect of three different surgical prone positions on lung volumes in healthy, awake volunteers, Hennessy, N., *et al.*, (*ARS*) 475P
——, Routine preoxygenation: how long before mask anaesthesia? Head-Rapson, A. G., *et al.*, (*ARS*) 488P

Malignant hyperthermia, Combined caffeine–halothane test for malignant hyperthermia, Ellis, F. R., *et al.*, (*C*) 598
——, Combined caffeine–halothane test for malignant hyperthermia, Nelson, T. E., (*C*) 597–598
——, Comparison of *in vitro* contracture testing with ryanodine, halothane and caffeine in malignant hyperthermia and other neuromuscular disorders, Hopkins, P. M., *et al.* 397–401
——, Exercise and malignant hyperthermia: family investigations, Kozak Ribbens, G., *et al.*, (*ESA*) A.92
——, Genetic linkage analysis of chromosome 19 markers in malignant hyperthermia, Ball, S. P., *et al.* 70–75
——, *In vitro* effect of ephedrine, adrenaline, noradrenaline and isoprenaline on halothane-induced contractures in skeletal muscle from patients potentially susceptible to malignant hyperthermia, Urwyler, A., *et al.* 76–79
——, Is Burkitt's lymphoma an etiology or a differential diagnosis of malignant hyperthermia? Lienhart, A., *et al.*, (*ESA*) A.93
——, Spin resonance spectroscopy to detect malignant hyperthermia susceptibility, Buckmaster, H. A., *et al.*, (*C*) 598–599
——, Spin resonance spectroscopy to detect malignant hyperthermia susceptibility, Halsall, P. J., *et al.*, (*C*) 599
Management of Acute Pain: A Practical Guide, Ready, L. B., *et al.*, (editors), (*R*) 495
MCQ for the Higher Examination in Clinical Pharmacology, McCarthy, G., *et al.*, (*R*) 241
MCQs in Anaesthesia: Basic Sciences, Kumar, B., (editor), (*R*) 117
Measurement techniques, airway reflexes, Effect of oral diazepam on the sensitivity of upper airway reflexes, Murphy, P. J., *et al.* 131–134
——, Measurement of the sensitivity of upper airway reflexes, Langton, J. A., *et al.* 126–130
Measurement techniques, arterial pressure, Clinical evaluation of the calibration of noninvasive continuous blood pressure measurement devices by means of oscillometric blood pressure measurements, de Jong, J. R., *et al.*, (*ESA*) A.15
——, Comparison of automatic oscillometric arterial pressure measurement with conventional auscultatory measurement in the labour ward, Hasan, M. A., *et al.* 141–144
Measurement techniques, carbon dioxide, Non invasive monitoring of CO_2 in patients with septic shock, Bodin, L., *et al.*, (*ESA*) A.191
Measurement techniques, cardiac output, Cardiac output (CO) measurement: comparison of esophageal Doppler

(ED) *vs* thermodilution (TD), Lefrant, J. Y., *et al.*, *(ESA)* A.18
——, Cardiac output determined from pulmonary gas exchange, Österlund, B., *et al.*, *(ESA)* A.19
——, Cardiovascular effects of i.v. induction in children: comparison between propofol and thiopentone, Aun, C. S. T., *et al.* 647–653
Measurement techniques, chemoluminescence, Benzodiazepines and their solvents influence neutrophil granulocyte function, Weiss, M., *et al.* 317–321
Measurement techniques, contracture test for MH, Combined caffeine–halothane test for malignant hyperthermia, Ellis, F. R., *et al.*, *(C)* 598
——, Combined caffeine–halothane test for malignant hyperthermia, Nelson, T. E., *(C)* 597–598
——, Comparison of *in vitro* contracture testing with ryanodine, halothane and caffeine in malignant hyperthermia and other neuromuscular disorders, Hopkins, P. M., *et al.* 397–401
——, *In vitro* effect of ephedrine, adrenaline, noradrenaline and isoprenaline on halothane-induced contractures in skeletal muscle from patients potentially susceptible to malignant hyperthermia, Urwyler, A., *et al.* 76–79
Measurement techniques, Doppler echocardiography, Cardiac output (CO) measurement: comparison of esophageal Doppler (ED) *vs* thermodilution (TD), Lefrant, J. Y., *et al.*, *(ESA)* A.18
——, Cardiovascular effects of i.v. induction in children: comparison between propofol and thiopentone, Aun, C. S. T., *et al.* 647–653
——, Incremental spinal anaesthesia for elective Caesarean section: maternal and fetal haemodynamic effects, Robson, S. C., *et al.* 634–638
Measurement techniques, drug concentration, *In vivo* determination of concentration–effect curves of local anaesthetics in man, Wiesemes, R., *et al.* 552–555
Measurement techniques, electron spin resonance, Spin resonance spectroscopy to detect malignant hyperthermia susceptibility, Buckmaster, H. A., *et al.*, *(C)* 598–599
——, Spin resonance spectroscopy to detect malignant hyperthermia susceptibility, Halsall, P. J., *et al.*, *(C)* 599
Measurement techniques, endoscopy, Studies of gastric content: comparison of two methods, Søreide, E., *et al.* 360–362
Measurement techniques, flowmetry, Effects of intradermal lignocaine and mepivacaine on human cutaneous circulation in areas with histamine-induced neurogenic inflammation, Fruhstorfer, H., *et al.* 167–172
Measurement techniques, mechanomyography, Tetanic fade during recovery from vecuronium block: comparison of systemic and isolated forearm administration, Campkin, N. T. A., *et al.* 581–582
Measurement techniques, microdialysis, Effects of midazolam and flunitrazepam on the release of dopamine from rat striatum measured by *in vivo* microdialysis, Takada, K., *et al.* 181–185
Measurement techniques, neuromuscular block, Comparison between double-burst stimulation and 50, 100 Hz tetanic fade during spontaneous recovery of vecuronium induced neuromuscular blockade, Baurain, M. J., *et al.*, *(ESA)* A.133
——, Potency estimation of mivacurium: comparison of two different modes of nerve stimulation, Maddineni, V. R., *et al.* 694–695
——, Recoveries of post-tetanic twitch and train-of-four responses after administration of vecuronium with different inhalation anaesthetics and neuroleptanaesthesia, Saitoh, Y., *et al.* 402–404
Measurement techniques, nuclear magnetic resonance, Visualization of extradural blood patch for post lumbar puncture headache by magnetic resonance imaging, Griffiths, A. G., *et al.* 223–225
Measurement techniques, oximeters, Preoxygenation and Sp_{O_2} after induction of anaesthesia with propofol and fentanyl, Rittoo, D. B., *et al.*, *(ARS)* 486P
——, Technical aspects of jugular bulb oximetry, De Deyne, C., *et al.*, *(ESA)* A.16
Measurement techniques, plethysmography, The effects of epidural and spinal anesthesia on the changes in the plethysmographic signal in the lower and upper limbs, Preisman, S., *et al.*, *(ESA)* A.124
Measurement techniques, spectral analysis, Accuracy of processed auditory evoked response in predicting movement during cardiac surgery, Kuppe, H., *et al.*, *(ESA)* A.31
Measurement techniques, thermodilution, Cardiac output (CO) measurement: comparison of esophageal Doppler (ED) *vs* thermodilution (TD), Lefrant, J. Y., *et al.*, *(ESA)* A.18
——, Cardiac output determined from pulmonary gas exchange, Österlund, B., *et al.*, *(ESA)* A.19
——, Comparison of thoracic electrical bioimpedance and thermodilution for the measurement of cardiac index in patients with severe sepsis, Young, J. D., *et al.* 58–62
Measurement techniques, thoracic impedance cardiography, Comparison of thoracic electrical bioimpedance and thermodilution for the measurement of cardiac index in patients with severe sepsis, Young, J. D., *et al.* 58–62
Measurement techniques, thrombelastography, Haemostasis and thrombelastography: a cautious note, Gupta, N. K., *et al.*, *(C)* 699
——, Haemostasis and thrombelastography: a cautious note, Mallett, S. V., *et al.*, *(C)* 699–700
Measurement techniques, tomography, Clinical and radiological comparison of perivascular and transarterial techniques of axillary brachial plexus block, Pere, P., *et al.* 276–279
Measurement techniques, transthoracic electrical impedance, Haemodynamic changes in patients undergoing laparoscopic cholecystectomy: measurement by transthoracic electrical bioimpedance, Critchley, L. A. H., *et al.* 681–683
Measurement techniques, tussometry, Laryngeal function as assessed by tussometry following topical anaesthesia, Mahajan, R. P., *et al.*, *(ESA)* A.68
——, Postoperative laryngeal function assessed by tussometry, Lamb, J. M., *et al.*, *(ARS)* 478–479P
Measurement techniques, ultrasound, Cerebral blood flow velocities (CBFV) during anaesthesia for gynaecological laparoscopic surgery, Granry, J. C., *et al.*, *(ESA)* A.32
——, Effect of nitrous oxide on cerebral blood flow in normal humans, Field, L. M., *et al.* 154–159
——, Hyperbaric decompression bubble formation—building on the Mapleson model of gas dynamics, Flook, V., *et al.*, *(ARS)* 474–475P
——, Incremental spinal anaesthesia for elective Caesarean section: maternal and fetal haemodynamic effects, Robson, S. C., *et al.* 634–638
——, Renal blood flow and function relationship in recent renal transplantation in man, Jacob, L., *et al.*, *(ESA)* A.85
——, Transcranial Doppler sonography: effect of propofol and thiopental in patients with brain tumors and brain injuries, Schregel, W., *et al.*, *(ESA)* A.105
——, Ultrasound measurement of muscle thickness in the estimation of fat free mass, Watt, T., *et al.*, *(ARS)* 477P
——, Use of ultrasound to evaluate internal jugular vein anatomy and to facilitate central venous cannulation in paediatric patients, Alderson, P. J., *et al.* 145–148
Medical Writing: A Prescription for Clarity, Goodman, N., *et al.*, (editors), *(R)* 385
Medico-legal, Death certification, Baskett, P. J. F., *(C)* 112
——, Death certification, Skinner, A. C., *(C)* 112
——, Spinal extradural abscess: pursuit of vigilance, Bromage, P. R. 471–473
Membrane, erythrocyte, Membrane action of volatile anaesthetics: effect of halothane on microviscosity, Appadu, B., *et al.*, *(ARS)* 477P
——, Spin resonance spectroscopy to detect malignant hyperthermia susceptibility, Buckmaster, H. A., *et al.*, *(C)* 598–599
——, Spin resonance spectroscopy to detect malignant hyperthermia susceptibility, Halsall, P. J., *et al.*, *(C)* 599
Membrane, lipid bilayers, Membrane action of volatile anaesthetics: effect of halothane on microviscosity, Appadu, B., *et al.*, *(ARS)* 477P
Membrane, nerve, Nitrous oxide induced neuronal depression: modification through benzodiazepine receptors, Dzoljic, M., *et al.*, *(ESA)* A.112
Memory, Comparison of the sedative and amnesic effects of midazolam and propofol, Polster, M. R., *et al.* 612–616
——, Flumazenil facilitates intraoperative arousal in scoliosis surgery, Koscielniak-Nielsen, Z. J., *et al.*, *(ESA)* A.157
——, Midazolam premedication: a forensic approach to pharmacokinetics and amnesia, Motsch, J., *et al.*, *(ESA)* A.155
——, Midazolam–alfentanil: an anaesthetic? An investigation using the isolated forearm technique, Russell, I. F. 42–46
——, Validation of coherent frequency of the EEG as a measure of consciousness during anaesthesia, Munglani, R., *et al.*, *(ARS)* 483–484P
Metabolism, energy expenditure, Metabolic effects of dobutamine, Campbell, I. T., *et al.*, *(C)* 236
——, Metabolic effects of dobutamine, Oh, T. E., *et al.*, *(C)* 237–238
——, Metabolic effects of dobutamine, Smith, D. C., *et al.*, *(C)* 236–237

Metabolism, fasting, How long should patients fast before surgery? Time for new guidelines, Strunin, L., (*E*) 1–3
——, Preoperative drinking and gastric contents, Levy, D. M., *et al.*, (*C*) 701–702
——, Preoperative drinking and gastric contents, Mather, C., (*C*) 702
——, Preoperative drinking and gastric contents, Phillips, S., *et al.*, (*C*) 702–703
——, Preoperative drinking and gastric contents, Read, M. S., *et al.*, (*C*) 701
——, Preoperative drinking and gastric contents, Strunin, L., (*C*) 702
——, Preoperative drinking does not affect gastric contents, Phillips, S., *et al.* 6–9
Metabolism, fluoride, Prolonged use of isoflurane in a patient with tetanus, Stevens, J. J. W. M., *et al.* 107–109
Metabolism, free radicals, Anaesthetic properties of dimethylthiourea, Koblin, D. D., *et al.* 456–458
——, Propofol (2,6 diisopropylphenol) as an antioxidant *in-vitro*: a dose response study, Bennett, S., *et al.*, (*ESA*) A.152
Metabolism, glucose, Effects of etomidate on the adrenocortical and metabolic adaptation of the neonate, Crozier, T. A., *et al.* 47–53
——, Isoflurane inhibits Ca^{2+}-induced insulin secretion from electrically permeabilised islets of Langerhans, Desborough, J. P., *et al.*, (*ESA*) A.91
——, Neonatal glycemia: does the maternal i.v. fluid regimen during labor make a difference? Menigaux, C., *et al.*, (*ESA*) A.175
Metabolism, glycine, Glycine and its metabolites during and after intrauterine YAG laser surgery, Van Boven, M. J., *et al.*, (*ESA*) A.87
Metabolism, isoflurane, Prolonged use of isoflurane in a patient with tetanus, Stevens, J. J. W. M., *et al.* 107–109
Metabolism, lactate, Changes in blood lactate, total body oxygen delivery and consumption during liver transplantation, Carrera, J., *et al.*, (*ESA*) A.77
——, Influence of norepinephrine therapy on the oxygen supply and lactate extraction rate of the liver in the septic pig, Schäfer, R., *et al.*, (*ESA*) A.184
——, Jugular bulb metabolic monitoring during hyperventilation in severe head trauma patients, De Deyne, C., *et al.*, (*ESA*) A.106
——, Sensitivity and specificity of mechanical and electrocardiographic myocardial ischaemia (MI) monitoring techniques, Hohner, P., *et al.*, (*ESA*) A.26
——, The use of the CUSUM plot for determination of myocardial ischaemia threshold during atrial pacing in patients with coronary artery disease, Reiz, S., *et al.*, (*ESA*) A.24
Metabolism, metabolites, Hepatotoxicity of volatile anaesthetics, Elliott, R. H., *et al.* 339–348
——, Lipid solubility of pancuronium and vecuronium determined by n-octanol/water partitioning, Weindlmayr-Goettel, M., *et al.* 579–580
Metabolism, midazolam, Midazolam premedication: a forensic approach to pharmacokinetics and amnesia, Motsch, J., *et al.*, (*ESA*) A.155
Metabolism, oxygen consumption, Effect of radiant heat on the metabolic cost of postoperative shivering, Sharkey, A., *et al.* 449–450
——, Influence of norepinephrine therapy on the oxygen supply and lactate extraction rate of the liver in the septic pig, Schäfer, R., *et al.*, (*ESA*) A.184
——, Metabolic effects of corrective surgery in infants and children with congenital heart defects, Puhakka, K., *et al.* 149–153
——, Metabolic effects of dobutamine, Campbell, I. T., *et al.*, (*C*) 236
——, Metabolic effects of dobutamine, Oh, T. E., *et al.*, (*C*) 237–238
——, Metabolic effects of dobutamine, Smith, D. C., *et al.*, (*C*) 236–237
——, Metabolic effects of propofol and flunitrazepam given for sedation after aortic surgery, Moritz, F., *et al.* 451–453
Metabolism, protein, Effect of recombinant human growth hormone (HGH) on protein metabolism in surgical patients, Carli, F., *et al.*, (*ESA*) A.86
Metabolism, protein, acute phase, Laparoscopic *vs* open cholecystectomy, Jakeways, M. S. R., *et al.*, (*C*) 597
——, Metabolic effects of cholecystectomy, Joris, J., (*C*) 494
——, Metabolic effects of cholecystectomy, McMahon, A. J., *et al.*, (*C*) 493–494
Microcirculation, Influence of N-acetylcysteine on O_2 consumption and gastric intramucosal pH in septic patients, Spies, C., *et al.*, (*ESA*) A.186
Model, acute pain service, Organization of acute pain services—a low-cost model, Rawal, N., (*ESA*) A.199
Model, computer simulation, Brain partial pressures of isoflurane and nitrous oxide, Petersen-Felix, S., *et al.*, (*C*) 704–705
——, Brain partial pressures of isoflurane and nitrous oxide, Thornton, C., *et al.*, (*C*) 705
——, Computer-controlled syringe pump improves safety of pharmacokinetic models, Duranteau, R., *et al.*, (*ESA*) A.148
Model, gas dynamics, Hyperbaric decompression bubble formation—building on the Mapleson model of gas dynamics, Flook, V., *et al.*, (*ARS*) 474–475P
Model, liver, Hepatic elimination of diazepam: interactions with albumin, desflurane and sevoflurane, Dale, O., *et al.* 454–455
Model, lung, Extra inspiratory work of breathing imposed by cricothyrotomy devices, Ooi, R., *et al.* 17–21
Model, mathematical, Evaluation in intensive care of the fraction area change obtained by automatic border detection, Liu, N., *et al.*, (*ESA*) A.25
——, Logistic regression analysis of fixed patient factors for postoperative sickness: a model for risk assessment, Palazzo, M., *et al.* 135–140
——, Mathematical analysis of the upper respiratory tract from an anthropometric study, Janvier, G., *et al.* 186–191
——, The use of the CUSUM plot for determination of myocardial ischaemia threshold during atrial pacing in patients with coronary artery disease, Reiz, S., *et al.*, (*ESA*) A.24
Model, membrane, Membrane action of volatile anaesthetics: effect of halothane on microviscosity, Appadu, B., *et al.*, (*ARS*) 477P
Model, neuroblastoma cells, Effect of fentanyl on [^{3}H]noradrenaline uptake in isolated neuronal cell preparations, Atcheson, R., *et al.*, (*ARS*) 485P
——, Effects of morphine and its metabolites on opiate receptor binding and cyclic adenosine-3′,5′-monophosphate (cAMP) formation in human neuroblastoma cells, Lambert, D. G., *et al.*, (*ARS*) 475–476P
——, Halothane enhances forskolin stimulated cyclic adenosine-3′,5′-monophosphate formation in human neuroblastoma cells, Hirst, R. A., *et al.*, (*ARS*) 486P
Model, pharmacodynamic, Pharmacokinetic/pharmacodynamic modelling of atracurium, Beemer, G. H., *et al.*, (*C*) 111
——, Pharmacokinetic/pharmacodynamic modelling of atracurium, Fisher, D. M., (*C*) 110–111
——, Pharmacokinetic/pharmacodynamic modelling of atracurium, Parker, C. J. R., *et al.*, (*C*) 111–112
Model, pharmacokinetic, Brain partial pressures of isoflurane and nitrous oxide, Petersen-Felix, S., *et al.*, (*C*) 704–705
——, Brain partial pressures of isoflurane and nitrous oxide, Thornton, C., *et al.*, (*C*) 705
——, Computer-controlled syringe pump improves safety of pharmacokinetic models, Duranteau, R., *et al.*, (*ESA*) A.148
——, Determination of a pharmacokinetic model for propofol induction of anaesthesia, Viviand, X., *et al.*, (*ESA*) A.150
——, Pharmacokinetic/pharmacodynamic modelling of atracurium, Beemer, G. H., *et al.*, (*C*) 111
——, Pharmacokinetic/pharmacodynamic modelling of atracurium, Fisher, D. M., (*C*) 110–111
——, Pharmacokinetic/pharmacodynamic modelling of atracurium, Parker, C. J. R., *et al.*, (*C*) 111–112
Model, pharmaco-physiological, A physiological model for the distribution of injected agents, with special reference to pethidine, Davis, N. R., *et al.* 248–258
——, Why not model physiologically? Sear, J. W., (*E*) 243–245
Model, rat, Hepatic elimination of diazepam: interactions with albumin, desflurane and sevoflurane, Dale, O., *et al.* 454–455
Model, water flea, Clonal variation in response to enflurane anaesthesia with *Daphnia magna*, Myles, A. P., *et al.*, (*ARS*) 476–477P
Monitoring, angiography, Dipyridamole-TEE and 24 h Holter-ECG as preoperative screening tests for coronary artery disease in patients with abdominal aortic aneurysm, Östman, M., *et al.*, (*ESA*) A.22
——, Does routine preoperative coronary angiography modify outcome after aortic surgery? Gosgnach, M., *et al.*, (*ESA*) A.6
——, Indications for coronary revascularisation in vascular surgical patients, Gosgnach, M., *et al.*, (*ESA*) A.5
Monitoring, body mass, Ultrasound measurement of muscle thickness in the estimation of fat free mass, Watt, T., *et al.*, (*ARS*) 477P
Monitoring, carbon dioxide, Non invasive monitoring of

CO_2 in patients with septic shock, Bodin, L., *et al.*, (*ESA*) A.191

Monitoring, cardiopulmonary, Comparison of thoracic electrical bioimpedance and thermodilution for the measurement of cardiac index in patients with severe sepsis, Young, J. D., *et al.* 58–62

Monitoring, computerized, Continuous monitoring of the ventilatory mechanics during anaesthesia & intensive care, Py, C., *et al.*, (*ESA*) A.57

——, Evaluation in intensive care of the fraction area change obtained by automatic border detection, Liu, N., *et al.*, (*ESA*) A.25

——, Sensitivity and specificity of mechanical and electrocardiographic myocardial ischaemia (MI) monitoring techniques, Hohner, P., *et al.*, (*ESA*) A.26

——, The use of the CUSUM plot for determination of myocardial ischaemia threshold during atrial pacing in patients with coronary artery disease, Reiz, S., *et al.*, (*ESA*) A.24

Monitoring, cuff pressure, Endobronchial cuff pressures, Cobley, M., *et al.* 576–578

Monitoring, depth of anaesthesia, Accuracy of processed auditory evoked response in predicting movement during cardiac surgery, Kuppe, H., *et al.*, (*ESA*) A.31

——, Effect of nitrous oxide on auditory evoked potentials, Jessop, J., *et al.*, (*C*) 380

——, Effect of nitrous oxide on auditory evoked potentials, Plourde, G., (*C*) 379–380

——, Midazolam–alfentanil: an anaesthetic? An investigation using the isolated forearm technique, Russell, I. F. 42–46

——, Validation of coherent frequency of the EEG as a measure of consciousness during anaesthesia, Munglani, R., *et al.*, (*ARS*) 483–484P

Monitoring, echocardiography, Cardiac function in aneurysmal subarachnoid haemorrhage, Moulay, N., *et al.*, (*ESA*) A.108

——, Determinants of systolic pressure variation in patients ventilated after vascular surgery, Beaussier, M., *et al.*, (*ESA*) A.37

——, Diagnosis of aortic rupture by transesophageal echocardiography (TEE), Goarin, J. P., *et al.*, (*ESA*) A.193

——, Dipyridamole-TEE and 24 h Holter-ECG as preoperative screening tests for coronary artery disease in patients with abdominal aortic aneurysm, Östman, M., *et al.*, (*ESA*) A.22

——, Echocardiographic study of the induction with a low-dose of sufentanil for coronary artery surgery, Bromberg, N., *et al.*, (*ESA*) A.28

——, Evaluation in intensive care of the fraction area change obtained by automatic border detection, Liu, N., *et al.*, (*ESA*) A.25

——, Evaluation of cardiac function in ICU: right heart catheterization *vs* transesophageal echocardiography. Preliminary results, Vivien, B., *et al.*, (*ESA*) A.183

——, Evaluation of systematic TEE in patients suspected of blunt chest trauma, Catoire, P., *et al.*, (*ESA*) A.192

——, Sensitivity and specificity of mechanical and electrocardiographic myocardial ischaemia (MI) monitoring techniques, Hohner, P., *et al.*, (*ESA*) A.26

——, Systemic gas embolism in pulmonary contusion diagnosed by transesophageal echocardiography, Saada, M., *et al.*, (*ESA*) A.194

——, Tolerance of preoperative transesophageal echocardiography in patients scheduled for aortic surgery, Gosgnach, M., *et al.*, (*ESA*) A.21

——, Transoesophageal echocardiographic assessment of haemodynamic function during laparoscopic cholecystectomy, Cunningham, A. J., *et al.* 621–625

——, Use of transoesophageal echocardiography to manage beta-adrenoceptor block and assess left ventricular function in a patient with phaeochromocytoma, Ryan, T., *et al.* 101–103

Monitoring, electrocardiography, Cardiac function in aneurysmal subarachnoid haemorrhage, Moulay, N., *et al.*, (*ESA*) A.108

——, Dipyridamole-TEE and 24 h Holter-ECG as preoperative screening tests for coronary artery disease in patients with abdominal aortic aneurysm, Östman, M., *et al.*, (*ESA*) A.22

——, Mechanisms of ECG changes during Caesarean section (CS)—a hypothesis, Svanström, M., *et al.*, (*ESA*) A.177

——, Sensitivity and specificity of mechanical and electrocardiographic myocardial ischaemia (MI) monitoring techniques, Hohner, P., *et al.*, (*ESA*) A.26

Monitoring, electroencephalography, EEG-monitoring during defibrillator-implantation: effects of repetitive cerebral ischemia on electric brain activity, Spies, C., *et al.*, (*ESA*) A.110

——, Spontaneous excitatory movements during recovery from propofol anaesthesia in an infant: EEG evaluation, Borgeat, A., *et al.* 459–461

——, Validation of coherent frequency of the EEG as a measure of consciousness during anaesthesia, Munglani, R., *et al.*, (*ARS*) 483–484P

Monitoring, electro-oculogram, Evaluation of saccadic eye movements as an objective test during recovery from anesthesia, Paut, O., *et al.*, (*ESA*) A.10

Monitoring, evoked potentials, Accuracy of processed auditory evoked response in predicting movement during cardiac surgery, Kuppe, H., *et al.*, (*ESA*) A.31

——, Effect of isometric thumb preload on the evoked compound muscle action potential, Kalli, I. 92–93

——, Effect of nitrous oxide on auditory evoked potentials, Jessop, J., *et al.*, (*C*) 380

——, Effect of nitrous oxide on auditory evoked potentials, Plourde, G., (*C*) 379–380

——, Validation of coherent frequency of the EEG as a measure of consciousness during anaesthesia, Munglani, R., *et al.*, (*ARS*) 483–484P

Monitoring, oxygen, Continuous monitoring of Sp_{O_2} during total intravenous anaesthesia with ketamine and spontaneous ventilation, Joly, L.-M., *et al.*, (*ESA*) A.58

——, Hypoxic events after general anaesthesia in the recovery room, Degasperi, D., *et al.*, (*ESA*) A.59

——, Technical aspects of jugular bulb oximetry, De Deyne, C., *et al.*, (*ESA*) A.16

Monitoring, spirometry, Continuous spirometry: an aid in the intraoperative respiratory monitoring—case reports, Bardoczky, G., *et al.*, (*ESA*) A.55

——, Continuous spirometry for detection of double-lumen endobronchial tube displacement, Bardoczky, G. I., *et al.* 499–502

Monitoring, sympathetic block, The effects of epidural and spinal anesthesia on the changes in the plethysmographic signal in the lower and upper limbs, Preisman, S., *et al.*, (*ESA*) A.124

Monitoring, ultrasound, Use of ultrasound to evaluate internal jugular vein anatomy and to facilitate central venous cannulation in paediatric patients, Alderson, P. J., *et al.* 145–148

Monitoring, vectorcardiography, Sensitivity and specificity of mechanical and electrocardiographic myocardial ischaemia (MI) monitoring techniques, Hohner, P., *et al.*, (*ESA*) A.26

——, The use of the CUSUM plot for determination of myocardial ischaemia threshold during atrial pacing in patients with coronary artery disease, Reiz, S., *et al.*, (*ESA*) A.24

Monitoring, ventilation, Continuous monitoring of the ventilatory mechanics during anaesthesia & intensive care, Py, C., *et al.*, (*ESA*) A.57

Mouse, Anaesthetic properties of dimethylthiourea, Koblin, D. D., *et al.* 456–458

——, Prejunctional action of neostigmine on mouse neuromuscular preparations, Braga, M. F. M., *et al.* 405–410

Muscle cardiac, contractility, Endocardial endothelium modulates *in vivo* left ventricular performance, De Hert, S. G., *et al.*, (*ESA*) A.47

——, Influence of cervicothoracic epidural anaesthesia (C-TEA) on left ventricular (LV) contractility—an experimental study in pigs with autonomous blockade, Reiz, S., *et al.*, (*ESA*) A.52

Muscle skeletal, Ultrasound measurement of muscle thickness in the estimation of fat free mass, Watt, T., *et al.*, (*ARS*) 477P

Muscle skeletal, contractility, *In vitro* effect of ephedrine, adrenaline, noradrenaline and isoprenaline on halothane-induced contractures in skeletal muscle from patients potentially susceptible to malignant hyperthermia, Urwyler, A., *et al.* 76–79

Muscle skeletal, diaphragm, Diaphragmatic function after bupivacaine cervical extradural analgesia for chronic pain therapy, Nyström, E., *et al.*, (*ESA*) A.65

Neonates, A bifurcated endobronchial tube in the management of laryngotracheo-oesophageal cleft repair, Ahmad, R., *et al.* 696–698

——, Effects of etomidate on the adrenocortical and metabolic adaptation of the neonate, Crozier, T. A., *et al.* 47–53

——, Extracorporeal membrane oxygenation for postoperative cardiac support in newborn infants: first clinical data, Marcassa, A., *et al.*, (*ESA*) A.168

——, Neonatal glycemia: does the maternal i.v. fluid regimen during labor make a difference? Menigaux, C., *et al.*, (*ESA*) A.175

——, Plasma catecholamines and neonatal condition after

induction of anaesthesia with propofol or thiopentone at Caesarean section, Gin, T., *et al.* 311–316
——, Use of ultrasound to evaluate internal jugular vein anatomy and to facilitate central venous cannulation in paediatric patients, Alderson, P. J., *et al.* 145–148
Nerve, damage (postoperative), Peripheral nerve damage and regional anaesthesia, Baranowski, A. P., *et al.*, (*C*) 593–594
——, Peripheral nerve damage and regional anaesthesia, Gentili, M. E., *et al.*, (*C*) 594
——, Peripheral nerve damage and regional anaesthesia, Rice, A. S. C., *et al.*, (*C*) 594
Nerve, differential block, Differential effects of alfentanil, fentanyl, pethidine and lignocaine administered intrathecally on nociceptive responses evoked by low and high frequency stimulation of somatic nerves, Wang, C., *et al.* 63–69
Nerve, membrane, Nitrous oxide induced neuronal depression: modification through benzodiazepine receptors, Dzoljic, M., *et al.*, (*ESA*) A.112
Nerve–muscle preparations, Prejunctional action of neostigmine on mouse neuromuscular preparations, Braga, M. F. M., *et al.* 405–410
Neuromuscular block, allergy, Platelet serotonin is a mediator potentially involved in anaphylactic reaction to neuromuscular blocking drugs, Bermejo, N., *et al.* 322–325
Neuromuscular block, Anq 9040, Anq 9040: effect of twice the ED$_{95}$ dose, Munday, I. T., *et al.*, (*ARS*) 480P
Neuromuscular block, antagonism, Neostigmine and edrophonium antagonism of moderate neuromuscular block induced by pancuronium or tubocurarine, Shorten, G. D., *et al.* 160–162
——, Prejunctional action of neostigmine on mouse neuromuscular preparations, Braga, M. F. M., *et al.* 405–410
——, Reversal of vecuronium induced neuromuscular blockade: no effects of atropine administration timing, Baurain, M. J., *et al.*, (*ESA*) A.134
Neuromuscular block, atracurium, Comparison of the onset of depolarizing *vs* non-depolarizing block after early tourniquet release in the isolated forearm, Hood, J. R., *et al.*, (*ARS*) 480P
——, Does nicardipine potentiate the neuromuscular block of atracurium? Bazin, J. E., *et al.*, (*ESA*) A.136
——, Effect of age, gender and anaesthetic technique on the pharmacodynamics of atracurium, Parker, C. J. R., *et al.* 38–41
——, Monitoring the onset of neuromuscular blockade at the orbicularis oculi can predict good intubating conditions when using 2 × ED$_{95}$ of atracurium, Debaene, B., *et al.*, (*ESA*) A.142
——, Mortality in ITU patients receiving neuromuscular blocking drugs, Hunter, J. M., *et al.*, (*C*) 238–239
——, Neostigmine antagonism of neuromuscular blockade induced by mivacurium, vecuronium and atracurium, Dernovoi, B. S., *et al.*, (*ESA*) A.137
——, Priming of atracurium with magnesium, Lampl, E., *et al.*, (*ESA*) A.139
——, Recovery of atracurium and vecuronium neuromuscular block in the isolated forearm, Law Min, J.-C., *et al.*, (*ARS*) 480–481P
——, Relationship between volume of distribution of atracurium and body weight, Parker, C. J. R., *et al.* 443–445
——, Supra-additivity between atracurium and vecuronium, Meretoja, O. A., *et al.*, (*ESA*) A.140
Neuromuscular block, decamethonium, Comparison of the onset of depolarizing *vs* non-depolarizing block after early tourniquet release in the isolated forearm, Hood, J. R., *et al.*, (*ARS*) 480P
Neuromuscular block, measurement of response, Can repetition of high frequencies stimuli alter the value of 50 and 100 Hz tetanic fade during vecuronium induced neuromuscular blockade? Baurain, M. J., *et al.*, (*ESA*) A.135
——, Comparison between double-burst stimulation and 50, 100 Hz tetanic fade during spontaneous recovery of vecuronium induced neuromuscular blockade, Baurain, M. J., *et al.*, (*ESA*) A.133
——, Monitoring the onset of neuromuscular blockade at the orbicularis oculi can predict good intubating conditions when using 2 × ED$_{95}$ of atracurium, Debaene, B., *et al.*, (*ESA*) A.142
——, Potency estimation of mivacurium: comparison of two different modes of nerve stimulation, Maddineni, V. R., *et al.* 694–695
Neuromuscular block, mivacurium, Neostigmine antagonism of neuromuscular blockade induced by mivacurium, vecuronium and atracurium, Dernovoi, B. S., *et al.*, (*ESA*) A.137
——, Neuromuscular blockade following mivacurium in children during N$_2$O–halothane, Orliaguet, G., *et al.*, (*ESA*) A.163
——, Pharmacokinetics of the isomers of mivacurium chloride in the healthy adult, Head-Rapson, A. G., *et al.*, (*ARS*) 487P
——, Potency estimation of mivacurium: comparison of two different modes of nerve stimulation, Maddineni, V. R., *et al.* 694–695
Neuromuscular block, pancuronium, Cardiovascular effects of a pancuronium–vecuronium mixture, Doyle, M., *et al.*, (*ARS*) 486–487P
——, Lipid solubility of pancuronium and vecuronium determined by n-octanol/water partitioning, Weindlmayr-Goettel, M., *et al.* 579–580
——, Neostigmine and edrophonium antagonism of moderate neuromuscular block induced by pancuronium or tubocurarine, Shorten, G. D., *et al.* 160–162
Neuromuscular block, pipecuronium, Pipecuronium-induced prolongation of vecuronium neuromuscular block, Smith, I., *et al.* 446–448
Neuromuscular block, potentiation, Does nicardipine potentiate the neuromuscular block of atracurium? Bazin, J. E., *et al.*, (*ESA*) A.136
——, Pipecuronium-induced prolongation of vecuronium neuromuscular block, Smith, I., *et al.* 446–448
——, Recoveries of post-tetanic twitch and train-of-four responses after administration of vecuronium with different inhalation anaesthetics and neuroleptanaesthesia, Saitoh, Y., *et al.* 402–404
Neuromuscular block, priming, Onset of action of a small dose of vecuronium, Nathanson, M. H., *et al.*, (*ARS*) 481–482P
——, Priming of atracurium with magnesium, Lampl, E., *et al.*, (*ESA*) A.139
Neuromuscular block, recovery, Can repetition of high frequencies stimuli alter the value of 50 and 100 Hz tetanic fade during vecuronium induced neuromuscular blockade? Baurain, M. J., *et al.*, (*ESA*) A.135
——, Comparison between double-burst stimulation and 50, 100 Hz tetanic fade during spontaneous recovery of vecuronium induced neuromuscular blockade, Baurain, M. J., *et al.*, (*ESA*) A.133
——, Neostigmine antagonism of neuromuscular blockade induced by mivacurium, vecuronium and atracurium, Dernovoi, B. S., *et al.*, (*ESA*) A.137
——, Neuromuscular blockers in day-case surgery: is speed of onset more important than duration of action? Lippmann, M., *et al.*, (*C*) 235
——, Neuromuscular blockers in day-case surgery: is speed of onset more important than duration of action? Mirakhur, R. K., *et al.*, (*C*) 235
——, Recoveries of post-tetanic twitch and train-of-four responses after administration of vecuronium with different inhalation anaesthetics and neuroleptanaesthesia, Saitoh, Y., *et al.* 402–404
——, Recovery of atracurium and vecuronium neuromuscular block in the isolated forearm, Law Min, J.-C., *et al.*, (*ARS*) 480–481P
——, Tetanic fade during recovery from vecuronium block: comparison of systemic and isolated forearm administration, Campkin, N. T. A., *et al.* 581–582
Neuromuscular block, rocuronium, Concentration–effect relationship at the vocal cords and the adductor pollicis following rocuronium administration, Plaud, B., *et al.*, (*ESA*) A.141
——, Neuromuscular blockers in day-case surgery: is speed of onset more important than duration of action? Lippmann, M., *et al.*, (*C*) 235
——, Neuromuscular blockers in day-case surgery: is speed of onset more important than duration of action? Mirakhur, R. K., *et al.*, (*C*) 235
——, Pharmacokinetics of rocuronium (Org 9426) in patients with and without impaired renal function, Cooper, R., *et al.*, (*ARS*) 482P
——, The pharmacokinetics of rocuronium in pediatric patients: a pooled data analysis, Meistelman, C., *et al.*, (*ESA*) A.138
Neuromuscular block, suxamethonium, Comparison of alfentanil with suxamethonium in facilitating nasotracheal intubation in day-case anaesthesia, Alcock, R., *et al.* 34–37
——, Propofol and alfentanil or thiopentone and suxamethonium for tracheal intubation, Beck, G. N., *et al.*, (*ARS*) 483P
Neuromuscular block, tubocurarine, Neostigmine and edrophonium antagonism of moderate neuromuscular

block induced by pancuronium or tubocurarine, Shorten, G. D., *et al.* 160–162
——, Prejunctional action of neostigmine on mouse neuromuscular preparations, Braga, M. F. M., *et al.* 405–410

Neuromuscular block, vecuronium, Can repetition of high frequencies stimuli alter the value of 50 and 100 Hz tetanic fade during vecuronium induced neuromuscular blockade? Baurain, M. J., *et al.*, (*ESA*) A.135
——, Cardiovascular effects of a pancuronium–vecuronium mixture, Doyle, M., *et al.*, (*ARS*) 486–487P
——, Comparison between double-burst stimulation and 50, 100 Hz tetanic fade during spontaneous recovery of vecuronium induced neuromuscular blockade, Baurain, M. J., *et al.*, (*ESA*) A.133
——, Comparison of the onset of depolarizing *vs* non-depolarizing block after early tourniquet release in the isolated forearm, Hood, J. R., *et al.*, (*ARS*) 480P
——, Lipid solubility of pancuronium and vecuronium determined by n-octanol/water partitioning, Weindlmayr-Goettel, M., *et al.* 579–580
——, Lung function after vecuronium pretreatment in elderly patients, Mahajan, R. P., *et al.*, (*ARS*) 482–483P
——, Neostigmine antagonism of neuromuscular blockade induced by mivacurium, vecuronium and atracurium, Dernovoi, B. S., *et al.*, (*ESA*) A.137
——, Neuromuscular blockers in day-case surgery: is speed of onset more important than duration of action? Lippmann, M., *et al.*, (*C*) 235
——, Neuromuscular blockers in day-case surgery: is speed of onset more important than duration of action? Mirakhur, R. K., *et al.*, (*C*) 235
——, Onset of action of a small dose of vecuronium, Nathanson, M. H., *et al.*, (*ARS*) 481–482P
——, Pipecuronium-induced prolongation of vecuronium neuromuscular block, Smith, I., *et al.* 446–448
——, Prediction of infusion rate of vecuronium to maintain steady state using the bolus test dose technique, Morgan, R. J., *et al.*, (*ARS*) 481P
——, Recoveries of post-tetanic twitch and train-of-four responses after administration of vecuronium with different inhalation anaesthetics and neuroleptanaesthesia, Saitoh, Y., *et al.* 402–404
——, Recovery of atracurium and vecuronium neuromuscular block in the isolated forearm, Law Min, J.-C., *et al.*, (*ARS*) 480–481P
——, Reversal of vecuronium induced neuromuscular blockade: no effects of atropine administration timing, Baurain, M. J., *et al.*, (*ESA*) A.134
——, Supra-additivity between atracurium and vecuronium, Meretoja, O. A., *et al.*, (*ESA*) A.140
——, Tetanic fade during recovery from vecuronium block: comparison of systemic and isolated forearm administration, Campkin, N. T. A., *et al.* 581–582

Neuromuscular transmission, Effect of isometric thumb preload on the evoked compound muscle action potential, Kalli, I. 92–93
——, Prejunctional action of neostigmine on mouse neuromuscular preparations, Braga, M. F. M., *et al.* 405–410
——, Tetanic fade during recovery from vecuronium block: comparison of systemic and isolated forearm administration, Campkin, N. T. A., *et al.* 581–582

Non-steroidal anti-inflammatory drugs, Diclofenac and ketoprofen for pain treatment after elective Caesarean section, Rorarius, M. G. F., *et al.* 293–297
——, Ketorolac postoperative analgesia, Al-Hasani, A., (*C*) 112–113
——, Ketorolac postoperative analgesia, Kinsella, J., (*C*) 113
——, Preoperative indomethacin for pain relief after thoracotomy: comparison with postoperative indomethacin, Murphy, D. F., *et al.* 298–300

Oxygen, consumption, Changes in blood lactate, total body oxygen delivery and consumption during liver transplantation, Carrera, J., *et al.*, (*ESA*) A.77
——, Influence of N-acetylcysteine on O_2 consumption and gastric intramucosal pH in septic patients, Spies, C., *et al.*, (*ESA*) A.186
——, Oxygen consumption is dependent upon oxygen delivery in cirrhotics undergoing liver transplantation, Piccinni, P., *et al.*, (*ESA*) A.78
——, The effect of dobutamine and norepinephrine on global and splanchnic O_2 consumption, Meier-Hellmann, A., *et al.*, (*ESA*) A.185

Oxygen, delivery systems, Comparison of nasal cannulae with face mask for oxygen administration to postoperative patients, Nolan, K. M., *et al.* 440–442
——, Extracorporeal membrane oxygenation for postoperative cardiac support in newborn infants: first clinical data, Marcassa, A., *et al.*, (*ESA*) A.168
——, IVOX, Skoyles, J., *et al.*, (*E*) 603–604

Oxygen, inspired concentration, Effect of hyperoxia on the breathing of patients anaesthetized with infusions of propofol, Dow, A. C., *et al.* 532–535
——, Effects of active and passive sighs in normoxia and hyperoxia on the breathing of patients anaesthetized with infusions of propofol, Goodman, N. W., *et al.* 536–541

Oxygen, measurement, Statistical assessment of two methods of clinical measurement, Berridge, J. C., (*C*) 595
——, Statistical assessment of two methods of clinical measurement, Runcie, C. J., (*C*) 595

Oxygen, saturation, Comparison of midazolam with propofol for sedation in outpatient bronchoscopy, Crawford, M., *et al.* 419–422
——, Continuous monitoring of Sp_{O_2} during total intravenous anaesthesia with ketamine and spontaneous ventilation, Joly, L.-M., *et al.*, (*ESA*) A.58
——, Effects of lorazepam on oxygen saturation before cardiac surgery, Pollock, J. S. S., *et al.* 219–220
——, Hypoxic events after general anaesthesia in the recovery room, Degasperi, D., *et al.*, (*ESA*) A.59
——, Influence of anaesthesia on post-operative hypoxaemia, Georgiou, L., *et al.*, (*ESA*) A.60
——, Jugular bulb metabolic monitoring during hyperventilation in severe head trauma patients, De Deyne, C., *et al.*, (*ESA*) A.106
——, Lung function after vecuronium pretreatment in elderly patients, Mahajan, R. P., *et al.*, (*ARS*) 482–483P
——, Preoxygenation and Sp_{O_2} after induction of anaesthesia with propofol and fentanyl, Rittoo, D. B., *et al.*, (*ARS*) 486P
——, Routine preoxygenation: how long before mask anaesthesia? Head-Rapson, A. G., *et al.*, (*ARS*) 488P
——, Sedation with propofol during regional anaesthesia, Arnold, B. D. C., (*C*) 112
——, Statistical assessment of two methods of clinical measurement, Berridge, J. C., (*C*) 595
——, Statistical assessment of two methods of clinical measurement, Runcie, C. J., (*C*) 595

Oxygen, therapy, Comparison of nasal cannulae with face mask for oxygen administration to postoperative patients, Nolan, K. M., *et al.* 440–442

Oxygen, tissue, Influence of norepinephrine therapy on the oxygen supply and lactate extraction rate of the liver in the septic pig, Schäfer, R., *et al.*, (*ESA*) A.184
——, Oxygen consumption is dependent upon oxygen delivery in cirrhotics undergoing liver transplantation, Piccinni, P., *et al.*, (*ESA*) A.78
——, The effect of dobutamine and norepinephrine on global and splanchnic O_2 consumption, Meier-Hellmann, A., *et al.*, (*ESA*) A.185

Oxygen, transport, The effect of dobutamine and norepinephrine on global and splanchnic O_2 consumption, Meier-Hellmann, A., *et al.*, (*ESA*) A.185

Oxygen, uptake, Propofol (2,6 diisopropylphenol) as an antioxidant *in-vitro*: a dose response study, Bennett, S., *et al.*, (*ESA*) A.152
——, Septic shock: effect of a goal-directed therapy on oxygen metabolism and serum cytokine levels, Martin, C., *et al.*, (*ESA*) A.189

Pain, Pre-emptive extradural analgesia, Hardy, P. A. J., (*C*) 493

Pain, acute, Intranasal fentanyl for breakthrough cancer pain or incident pain, Striebel, W. H., *et al.*, (*ESA*) A.210
——, Organization of acute pain services—a low-cost model, Rawal, N., (*ESA*) A.199
——, The value of pre-emptive analgesia in the treatment of postoperative pain, Dahl, J. B., *et al.* 434–439

Pain, chronic, Diaphragmatic function after bupivacaine cervical extradural analgesia for chronic pain therapy, Nyström, E., *et al.*, (*ESA*) A.65
——, High dose oral morphine in cancer pain management, Radbruch, L., *et al.*, (*ESA*) A.212
——, Intranasal fentanyl for breakthrough cancer pain or incident pain, Striebel, W. H., *et al.*, (*ESA*) A.210
——, Intrathecal pain relief in terminally ill cancer patients at home, Wagemans, M. F. M., *et al.*, (*ESA*) A.213
——, Treatment of cancer pain with morphine (MO)—A double blind study of extradural (ED) *versus* intramuscular (im) routes of administration, Nath, S., *et al.*, (*ESA*) A.211

Pain, injection, Alizapride does reduce pain on injection of propofol: comparison with lidocaine, Zaouk, G., *et al.*, (*ESA*) A.11

——, Pain on i.v. injection of metoclopramide, Wilkinson, D. J., *(C)* 239
——, Quality of induction: a clinical comparison of Etomidat-Lipuro® and Hypnomidate®, Wiebalck, A., *et al.*, *(ESA)* A.154
Pain, mechanism, Differential effects of specific delta and kappa opioid antagonists on the bidirectionnal effect of naloxone in arthritic rats, Cattaneo, I., *et al.*, *(ESA)* A.114
——, Pre-emptive analgesia, Dahl, J. B., *et al.*, *(C)* 379
——, Pre-emptive analgesia, Katz, J., *et al.*, *(C)* 378
——, The value of pre-emptive analgesia in the treatment of postoperative pain, Dahl, J. B., *et al.* 434–439
Pain, postoperative, A survey of sleep problems in surgical patients, Beydon, L., *et al.*, *(ESA)* A.4
——, Addition of droperidol to PCA morphine: what is the optimal dose? Lamond, C. T., *et al.*, *(ESA)* A.204
——, Analgesia by wound infiltration before or after surgery in inguinal hernioraphy, Hennart, D., *et al.*, *(ESA)* A.202
——, Diclofenac and ketoprofen for pain treatment after elective Caesarean section, Rorarius, M. G. F., *et al.* 293–297
——, Effect of morphine on a nociceptive flexion reflex in patients with postoperative pain, Chauvin, M., *et al.*, *(ESA)* A.115
——, Efficacy of continuous intercostal bupivacaine for pain relief after thoracotomy, Dryden, C. M., *et al.* 508–510
——, Efficacy of postoperative pain treatment regimens using both buprenorphine and papaveretum sequentially after abdominal hysterectomy, Green, D. W., *et al.* 626–630
——, Epidural administration of liposomal bupivacaine for the management of postsurgical pain, Boogaerts, J., *et al.*, *(ESA)* A.200
——, Epidural clonidine analgesia after major gynaecological surgery, Smilov, I., *et al.*, *(ESA)* A.176
——, Evaluation of pain and analgesia in a postanesthesia care unit, Aubrun, F., *et al.*, *(ESA)* A.198
——, Evaluation of the analgesic effect of metoclopramide after opioid-free analgesia, Lisander, B. 631–633
——, Extradural 0.07% bupivacaine for postoperative pain, Slade, J. M., *(ARS)* 478P
——, Intranasal fentanyl for postoperative pain management in an unselected population, Striebel, W. H., *et al.*, *(ESA)* A.209
——, Ketorolac postoperative analgesia, Al-Hasani, A., *(C)* 112–113
——, Ketorolac postoperative analgesia, Kinsella, J., *(C)* 113
——, Organization of acute pain services—a low-cost model, Rawal, N., *(ESA)* A.199
——, Pain relief after anterior cruciate ligament repair, Carroll, P. H., *et al.*, *(C)* 600
——, Pain relief after anterior cruciate ligament repair, Joshi, G. P., *(C)* 600
——, Pain relief for infants undergoing abdominal surgery: comparison of infusions of i.v. morphine and extradural bupivacaine, Wolf, A. R., *et al.* 10–16
——, Partial reversal of the effects of extradural clonidine by oral yohimbine in postoperative patients, Liu, N., *et al.* 515–518
——, Patient-controlled extradural analgesia to compare bupivacaine, fentanyl and bupivacaine with fentanyl in the treatment of postoperative pain, Cooper, D. W., *et al.* 503–507
——, Postoperative analgesia: a two dosage regimens trial for i.m. morphine after early i.v. titration, Butscher, K., *et al.*, *(ESA)* A.201
——, Postoperative analgesia in children, Fell, D., *(E)* 4–5
——, Postoperative pain thresholds, Cook, T. M., *(C)* 110
——, Pre-emptive analgesia, Dahl, J. B., *et al.*, *(C)* 379
——, Pre-emptive analgesia, Katz, J., *et al.*, *(C)* 378
——, Preemptive analgesia with epidural morphine, Nègre, I., *et al.*, *(ESA)* A.203
——, Preoperative indomethacin for pain relief after thoracotomy: comparison with postoperative indomethacin, Murphy, D. F., *et al.* 298–300
——, The value of pre-emptive analgesia in the treatment of postoperative pain, Dahl, J. B., *et al.* 434–439
——, Transthoracic endoscopic sympathectomy, Gilligan, S., *et al.*, *(C)* 491
——, Transthoracic endoscopic sympathectomy, Jedeiken, R., *et al.*, *(C)* 491–492
——, Transthoracic endoscopic sympathectomy, Plastow, S. E., *et al.*, *(C)* 492
——, Ventilatory effects of morphine, pethidine and methadone in children, Hamunen, K. 414–418
Pain, threshold, Alterations in pain threshold and psychomotor response associated with subanaesthetic concentrations of inhalation anaesthetics in humans, Tomi, K., *et al.* 684–686
——, *In vivo* determination of concentration–effect curves of local anaesthetics in man, Wiesemes, R., *et al.* 552–555
——, Postoperative pain thresholds, Cook, T. M., *(C)* 110
Pain, tourniquet, Comparison of the effect of EMLA cream, subcutaneous ring anaesthesia and a double cuff technique in the prevention of tourniquet pain, Tsai, Y.-C., *et al.* 394–396
Pain, visceral, Direct spinal effect of intrathecal and extradural midazolam on visceral noxious stimulation in rabbits, Crawford, M. E., *et al.* 642–646
Parasympathetic nervous system, Effects of surgical stimulation on autonomic reflex function: assessment by changes in heart rate variability, Latson, T. W., *et al.* 301–305
Parasympathetic nervous system, atropine, Reversal of vecuronium induced neuromuscular blockade: no effects of atropine administration timing, Baurain, M. J., *et al.*, *(ESA)* A.134
Parasympathetic nervous system, glycopyrronium, Glycopyrronium prolongs topical anaesthesia of oral mucosa and enhances absorption of lignocaine, Watanabe, H., *et al.* 94–95
Partial pressure, arterial–end-tidal, Components of the inspiratory–arterial isoflurane partial pressure difference, Landon, A. J., *et al.* 605–611
——, Relationship between arterial $P\text{co}_2$ (Pa_{CO_2}) and end tidal CO_2 (ETco_2) recorded through a laryngeal mask (LMA) in children breathing spontaneously, Van Obbergh, L. J., *et al.*, *(ESA)* A.164
Partial pressure, carbon dioxide, Is correlation of arterial and end-tidal carbon dioxide pressure during inhalation anaesthesia better with laryngeal mask as compared to face mask? Ivens, D., *et al.*, *(ESA)* A.17
Partial pressure, inert gases, Asymmetry of uptake and washout of inert gases—lessons learnt in an anaesthetic department, Flook, V., *(ARS)* 487–488P
——, Hyperbaric decompression bubble formation—building on the Mapleson model of gas dynamics, Flook, V., *et al.*, *(ARS)* 474–475P
Partial pressure, isoflurane, Brain partial pressures of isoflurane and nitrous oxide, Petersen-Felix, S., *et al.*, *(C)* 704–705
——, Brain partial pressures of isoflurane and nitrous oxide, Thornton, C., *et al.*, *(C)* 705
——, Components of the inspiratory–arterial isoflurane partial pressure difference, Landon, A. J., *et al.* 605–611
Partial pressure, nitrous oxide, Brain partial pressures of isoflurane and nitrous oxide, Petersen-Felix, S., *et al.*, *(C)* 704–705
——, Brain partial pressures of isoflurane and nitrous oxide, Thornton, C., *et al.*, *(C)* 705
Partial pressure, oxygen, Early postperfusion assessment of gas exchange and postoperative extubation outcome following coronary artery surgery, Knapik, P., *et al.*, *(ESA)* A.61
Phaeochromocytoma, Use of transoesophageal echocardiography to manage beta-adrenoceptor block and assess left ventricular function in a patient with phaeochromocytoma, Ryan, T., *et al.* 101–103
Pharmacodynamics, Comparison of the onset of depolarizing *vs* non-depolarizing block after early tourniquet release in the isolated forearm, Hood, J. R., *et al.*, *(ARS)* 480P
——, Concentration–effect relationship at the vocal cords and the adductor pollicis following rocuronium administration, Plaud, B., *et al.*, *(ESA)* A.141
——, Effect of age, gender and anaesthetic technique on the pharmacodynamics of atracurium, Parker, C. J. R., *et al.* 38–41
——, I.v. bolus administration of subconvulsive doses of lignocaine to conscious sheep: relationships between myocardial pharmacokinetics and pharmacodynamics, Huang, Y. F., *et al.* 556–561
——, Monitoring the onset of neuromuscular blockade at the orbicularis oculi can predict good intubating conditions when using $2 \times \text{ED}_{95}$ of atracurium, Debaene, B., *et al.*, *(ESA)* A.142
——, Neuromuscular blockade following mivacurium in children during N_2O–halothane, Orliaguet, G., *et al.*, *(ESA)* A.163
——, Neuromuscular blockers in day-case surgery: is speed of onset more important than duration of action? Lippmann, M., *et al.*, *(C)* 235
——, Neuromuscular blockers in day-case surgery: is speed of onset more important than duration of action? Mirakhur, R. K., *et al.*, *(C)* 235
——, Onset of action of a small dose of vecuronium, Nathanson, M. H., *et al.*, *(ARS)* 481–482P

——, Pharmacokinetic/pharmacodynamic modelling of atracurium, Beemer, G. H., *et al.*, (*C*) 111
——, Pharmacokinetic/pharmacodynamic modelling of atracurium, Fisher, D. M., (*C*) 110–111
——, Pharmacokinetic/pharmacodynamic modelling of atracurium, Parker, C. J. R., *et al.*, (*C*) 111–112
——, Pharmacokinetics and pharmacodynamics of ketamine enantiomers in surgical patients using a stereoselective analytical method, Geisslinger, G., *et al.* 666–671
——, Propofol and alfentanil mixture, Sandin, R., (*C*) 382–383
——, Propofol and alfentanil mixture, Taylor, I. N., *et al.*, (*C*) 383
——, Relationship between volume of distribution of atracurium and body weight, Parker, C. J. R., *et al.* 443–445
Pharmacokinetics, alfentanil, Pharmacokinetic behaviour of transdermal fentanyl, Van Bastelaere, M., *et al.*, (*ESA*) A.146
——, Pharmacokinetics and effects of i.m. alfentanil as premedication for outpatient cataract surgery, Ali-Melkkilä, T., *et al.*, (*ESA*) A.145
Pharmacokinetics, atracurium, Mortality in ITU patients receiving neuromuscular blocking drugs, Hunter, J. M., *et al.*, (*C*) 238–239
——, Pharmacokinetic/pharmacodynamic modelling of atracurium, Beemer, G. H., *et al.*, (*C*) 111
——, Pharmacokinetic/pharmacodynamic modelling of atracurium, Fisher, D. M., (*C*) 110–111
——, Pharmacokinetic/pharmacodynamic modelling of atracurium, Parker, C. J. R., *et al.*, (*C*) 111–112
——, Relationship between volume of distribution of atracurium and body weight, Parker, C. J. R., *et al.* 443–445
Pharmacokinetics, bupivacaine, Plasma concentrations of bupivacaine and its enantiomers during continuous extrapleural intercostal nerve block, Berrisford, R. G., *et al.* 201–204
——, Slow-release effect of pH-adjusted bupivacaine: pharmacokinetic demonstration, Benhamou, D., *et al.*, (*ESA*) A.120
Pharmacokinetics, fentanyl, Pharmacokinetics of intranasal fentanyl, Striebel, H. W., *et al.*, (*ESA*) A.208
Pharmacokinetics, flumazenil, Pharmacokinetics of flumazenil and midazolam, Jones, R. D. M., *et al.* 286–292
Pharmacokinetics, glycine, Glycine and its metabolites during and after intrauterine YAG laser surgery, Van Boven, M. J., *et al.*, (*ESA*) A.87
Pharmacokinetics, heart, I.v. bolus administration of subconvulsive doses of lignocaine to conscious sheep: myocardial pharmacokinetics, Huang, Y. F., *et al.* 326–332
——, I.v. bolus administration of subconvulsive doses of lignocaine to conscious sheep: relationships between myocardial pharmacokinetics and pharmacodynamics, Huang, Y. F., *et al.* 556–561
Pharmacokinetics, ketamine, Pharmacokinetics and pharmacodynamics of ketamine enantiomers in surgical patients using a stereoselective analytical method, Geisslinger, G., *et al.* 666–671
Pharmacokinetics, lignocaine, I.v. bolus administration of subconvulsive doses of lignocaine to conscious sheep: myocardial pharmacokinetics, Huang, Y. F., *et al.* 326–332
——, I.v. bolus administration of subconvulsive doses of lignocaine to conscious sheep: relationships between myocardial pharmacokinetics and pharmacodynamics, Huang, Y. F., *et al.* 556–561
Pharmacokinetics, liver, Pharmacokinetics of rocuronium (Org 9426) in patients with and without impaired renal function, Cooper, R., *et al.*, (*ARS*) 482P
Pharmacokinetics, lung, Sufentanil first-pass pulmonary uptake at three different steady state concentrations of the drug, Boer, F., *et al.*, (*ESA*) A.147
Pharmacokinetics, midazolam, Midazolam premedication: a forensic approach to pharmacokinetics and amnesia, Motsch, J., *et al.*, (*ESA*) A.155
——, Pharmacokinetics of flumazenil and midazolam, Jones, R. D. M., *et al.* 286–292
——, Prolonged (> 1 week) sedation with midazolam in ICU patients: efficacy, safety and pharmacokinetics, Heytens, L., *et al.*, (*ESA*) A.178
Pharmacokinetics, mivacurium, Pharmacokinetics of the isomers of mivacurium chloride in the healthy adult, Head-Rapson, A. G., *et al.*, (*ARS*) 487P
Pharmacokinetics, models, A physiological model for the distribution of injected agents, with special reference to pethidine, Davis, N. R., *et al.* 248–258
——, Effect of age, gender and anaesthetic technique on the pharmacodynamics of atracurium, Parker, C. J. R., *et al.* 38–41
——, Why not model physiologically? Sear, J. W., (*E*) 243–245
Pharmacokinetics, morphine-6-glucuronide, Morphine-6-glucuronide disposition in renal impairment, Hanna, M. H., *et al.* 511–514
Pharmacokinetics, obesity, Perioperative management of the obese patient, Shenkman, Z., *et al.* 349–359
Pharmacokinetics, propofol, Pharmacokinetics of propofol administered by infusion in dogs undergoing surgery, Nolan, A., *et al.* 546–551
——, Pharmacokinetics of propofol and its conjugates after continuous infusion in normal and renal failure patients, Nathan, N., *et al.*, (*ESA*) A.151
Pharmacokinetics, rocuronium, Concentration–effect relationship at the vocal cords and the adductor pollicis following rocuronium administration, Plaud, B., *et al.*, (*ESA*) A.141
——, Pharmacokinetics of rocuronium (Org 9426) in patients with and without impaired renal function, Cooper, R., *et al.*, (*ARS*) 482P
——, The pharmacokinetics of rocuronium in pediatric patients: a pooled data analysis, Meistelman, C., *et al.*, (*ESA*) A.138
Pharmacokinetics, solubility, Lipid solubility of pancuronium and vecuronium determined by n-octanol/water partitioning, Weindlmayr-Goettel, M., *et al.* 579–580
Pharmacokinetics, stereoisomers, Pharmacokinetics and pharmacodynamics of ketamine enantiomers in surgical patients using a stereoselective analytical method, Geisslinger, G., *et al.* 666–671
——, Pharmacokinetics of the isomers of mivacurium chloride in the healthy adult, Head-Rapson, A. G., *et al.*, (*ARS*) 487P
——, Plasma concentrations of bupivacaine and its enantiomers during continuous extrapleural intercostal nerve block, Berrisford, R. G., *et al.* 201–204
Pharmacokinetics, uptake, Components of the inspiratory–arterial isoflurane partial pressure difference, Landon, A. J., *et al.* 605–611
——, Influence of cardiac output, injection time and injection volume on the initial mixing of drugs with venous blood after i.v. bolus administration to sheep, Upton, R. N., *et al.* 333–338
——, Onset of action of a small dose of vecuronium, Nathanson, M. H., *et al.*, (*ARS*) 481–482P
——, Plasma concentrations of midazolam after i.v., nasal or rectal administration in children, Malinovsky, J.-M., *et al.* 617–620
——, Relationship between volume of distribution of atracurium and body weight, Parker, C. J. R., *et al.* 443–445
——, Sufentanil first-pass pulmonary uptake at three different steady state concentrations of the drug, Boer, F., *et al.*, (*ESA*) A.147
——, The pharmacokinetics of rocuronium in pediatric patients: a pooled data analysis, Meistelman, C., *et al.*, (*ESA*) A.138
——, Ultrasound measurement of muscle thickness in the estimation of fat free mass, Watt, T., *et al.*, (*ARS*) 477P
Pharmacology, 5-HT antagonists, Comparison of ondansetron, metoclopramide and droperidol for the prophylaxis of emetic symptoms after gynecological laparoscopic procedures, Geiger, C., *et al.*, (*ESA*) A.14
——, Double-blind comparison of ondansetron, droperidol and saline for prevention of nausea & vomiting after orthopaedic surgery, Gan, T. J., *et al.*, (*ESA*) A.13
——, Ondansetron 4 mg *vs* droperidol 1.25 mg in the prophylaxis of postoperative nausea and vomiting after alfentanil-supplemented inhalation anaesthesia, Alon, E., *et al.*, (*ESA*) A.12
Pharmacology, alizapride, Alizapride does reduce pain on injection of propofol: comparison with lidocaine, Zaouk, G., *et al.*, (*ESA*) A.11
Pharmacology, blood loss, Perioperative blood loss, Appadu, B., (*C*) 492–493
Pharmacology, bupivacaine, Motor blockade and absence of local nerve toxicity induced by liposomal bupivacaine injected into the axillary brachial plexus of rabbits, Legros, F. J., *et al.*, (*ESA*) A.122
Pharmacology, captopril, Does captopril modify the arterial response to vasopressor substances? Le Pelley, E., *et al.*, (*ESA*) A.48
Pharmacology, clonidine, Clonidine in paediatric caudal anaesthesia, Jamali, S., *et al.*, (*ESA*) A.160
——, Effects of epidural clonidine on anaesthetic requirements and postoperative analgesia, Samsó, E., *et al.*, (*ESA*) A.205
——, Epidural clonidine and myocardial ischaemia after

abdominal aortic surgery, Fulgencio, J. P., *et al.*, (*ESA*) A.42
——, Partial reversal of the effects of extradural clonidine by oral yohimbine in postoperative patients, Liu, N., *et al.* 515–518
——, Preoperative clonidine improves postoperative renal function in CABG patients, Kulka, P. J., *et al.*, (*ESA*) A.143
Pharmacology, dexmedetomidine, Dexmedetomidine does not exercise its anesthetic action through GABA, Salonen, M., *et al.*, (*ESA*) A.113
Pharmacology, dimethylthiourea, Anaesthetic properties of dimethylthiourea, Koblin, D. D., *et al.* 456–458
Pharmacology, dobutamine, Metabolic effects of dobutamine, Campbell, I. T., *et al.*, (*C*) 236
——, Metabolic effects of dobutamine, Oh, T. E., *et al.*, (*C*) 237–238
——, Metabolic effects of dobutamine, Smith, D. C., *et al.*, (*C*) 236–237
Pharmacology, dose-response, *In vivo* determination of concentration–effect curves of local anaesthetics in man, Wiesemes, R., *et al.* 552–555
——, Potency estimation of mivacurium: comparison of two different modes of nerve stimulation, Maddineni, V. R., *et al.* 694–695
——, Propofol (2,6 diisopropylphenol) as an antioxidant *in-vitro*: a dose response study, Bennett, S., *et al.*, (*ESA*) A.152
Pharmacology, enoximone, Haemodynamic changes produced by inhalation anaesthetics in the presence of phosphodiesterase inhibition, Molter, G., *et al.* 428–433
Pharmacology, guanfacine, Effects of oral preoperative guanfacine on anesthetics requirements, Engelman, E., *et al.*, (*ESA*) A.144
Pharmacology, isoboles, Synergy and isoboles, Calvey, T. N., (*E*) 246–247
Pharmacology, lemakalim, Lemakalim reverses ventricular conduction impairment induced by a large dose of bupivacaine in anesthetized dogs, de La Coussaye, J. E., *et al.*, (*ESA*) A.121
Pharmacology, metoclopramide, Evaluation of the analgesic effect of metoclopramide after opioid-free analgesia, Lisander, B. 631–633
——, Pain on i.v. injection of metoclopramide, Wilkinson, D. J., (*C*) 239
Pharmacology, midazolam, Direct spinal effect of intrathecal and extradural midazolam on visceral noxious stimulation in rabbits, Crawford, M. E., *et al.* 642–646
Pharmacology, morphine, Treatment of cancer pain with morphine (MO)—A double blind study of extradural (ED) *versus* intramuscular (im) routes of administration, Nath, S., *et al.*, (*ESA*) A.211
Pharmacology, N-acetylcysteine, Influence of N-acetylcysteine on O_2 consumption and gastric intramucosal pH in septic patients, Spies, C., *et al.*, (*ESA*) A.186
Pharmacology, phosphodiesterase inhibitors, Haemodynamic changes produced by inhalation anaesthetics in the presence of phosphodiesterase inhibition, Molter, G., *et al.* 428–433
Pharmacology, preservatives, Functional recovery after 24 h preservation of rabbit hearts in University Wisconsin solution, Fellahi, J. L., *et al.*, (*ESA*) A.44
Pharmacology, propofol, Propofol (2,6 diisopropylphenol) as an antioxidant *in-vitro*: a dose response study, Bennett, S., *et al.*, (*ESA*) A.152
Pharmacology, ryanodine, Comparison of *in vitro* contracture testing with ryanodine, halothane and caffeine in malignant hyperthermia and other neuromuscular disorders, Hopkins, P. M., *et al.* 397–401
Pharmacology, sodium bicarbonate, Acute haemodynamic effect of sodium bicarbonate in canine respiratory or metabolic acidosis, Nishikawa, T. 196–200
Pharmacology, synergism, Dexmedetomidine does not exercise its anesthetic action through GABA, Salonen, M., *et al.*, (*ESA*) A.113
——, Does exogenous dopamine reverse cardiovascular depression induced by isoflurane during thoracic epidural blockade? Raner, C., *et al.*, (*ESA*) A.49
——, Effect of age, gender and anaesthetic technique on the pharmacodynamics of atracurium, Parker, C. J. R., *et al.* 38–41
——, Supra-additivity between atracurium and vecuronium, Meretoja, O. A., *et al.*, (*ESA*) A.140
——, Synergy and isoboles, Calvey, T. N., (*E*) 246–247
Pharmacology, vecuronium, Tetanic fade during recovery from vecuronium block: comparison of systemic and isolated forearm administration, Campkin, N. T. A., *et al.* 581–582
Pharmacology, yohimbine, Partial reversal of the effects of extradural clonidine by oral yohimbine in postoperative patients, Liu, N., *et al.* 515–518
Physics, baricity, Hypertonic solutions in acute massive haemorrhage, Brimacombe, J., *et al.*, (*C*) 705
——, Hypertonic solutions in acute massive haemorrhage, Park, G. R., (*C*) 706
Physics, fluid dynamics, Evidence for dynamic phenomena in residual tracheal tube biofilm, Inglis, T. J. J. 22–24
Pig, Aprotinin does not decrease surgical bleeding and could promote arterial thrombosis in the pig: a prospective randomized, blind, study, Samama, C. M., *et al.*, (*ESA*) A.100
——, Does captopril modify the arterial response to vasopressor substances? Le Pelley, E., *et al.*, (*ESA*) A.48
——, Influence of cervicothoracic epidural anaesthesia (C-TEA) on left ventricular (LV) contractility—an experimental study in pigs with autonomous blockade, Reiz, S., *et al.*, (*ESA*) A.52
——, Influence of norepinephrine therapy on the oxygen supply and lactate extraction rate of the liver in the septic pig, Schäfer, R., *et al.*, (*ESA*) A.184
——, Midazolam prevents ketamine-induced stimulation of cerebral metabolism, Åkeson, J., *et al.*, (*ESA*) A.111
——, Pre- and intraoperative prevention by β-blockers, propranolol and esmolol, of ischaemia-induced ventricular fibrillation, Freysz, M., *et al.*, (*ESA*) A.46
Placenta, drug distribution, Intermittent *vs* continuous extradural infusion of bupivacaine during labour, Laishley, R. S., (*C*) 490
Polypeptides, aprotinin, Aprotinin does not decrease surgical bleeding and could promote arterial thrombosis in the pig: a prospective randomized, blind, study, Samama, C. M., *et al.*, (*ESA*) A.100
——, Blood requirements reduction in orthotopic liver transplantation with aprotinin, Monedero, P., *et al.*, (*ESA*) A.98
——, High dose aprotinin *versus* desmo-pressin acetate treatment in cardiac surgery, Hidalgo, F., *et al.*, (*ESA*) A.99
——, Use of aprotinine during cytoreductive surgery of ovarian cancer, Lequeau, F., *et al.*, (*ESA*) A.97
Polypeptides, cytokines, Laparoscopic *vs* open cholecystectomy, Jakeways, M. S. R., *et al.*, (*C*) 597
——, Metabolic effects of cholecystectomy, Joris, J., (*C*) 494
——, Metabolic effects of cholecystectomy, McMahon, A. J., *et al.*, (*C*) 493–494
——, Molecular mediators and cardiac surgery, Pérez Arancón, J. L., *et al.*, (*ESA*) A.188
——, Molecular mediators and post-bacteraemic phase, Martínez Urionabarrenetxea, K., *et al.*, (*ESA*) A.187
——, Septic shock: effect of a goal-directed therapy on oxygen metabolism and serum cytokine levels, Martin, C., *et al.*, (*ESA*) A.189
Polypeptides, endothelin, Is the vasoconstrictive effect of cyclosporine mediated by endothelin in kidney transplantation? Mouquet, C., *et al.*, (*ESA*) A.84
Porphyria, Xylometazoline and porphyria, Platt, N. D., (*C*) 491
Position, effects, Influence of pneumoperitoneum and posture on hemodynamic and stress responses during anaesthesia for laparoscopic surgery, Odeberg, S., *et al.*, (*ESA*) A.34
——, Influence of posture on the respiratory mechanics during anesthesia, Engelman, E., *et al.*, (*ESA*) A.56
Position, head, Influence of posture on the respiratory mechanics during anesthesia, Engelman, E., *et al.*, (*ESA*) A.56
Position, lithotomy, Fresh gas requirements of an enclosed afferent reservoir breathing system in anaesthetized, spontaneously breathing adults, Barrie, J. R., *et al.* 468–470
Position, prone, Effect of three different surgical prone positions on lung volumes in healthy, awake volunteers, Hennessy, N., *et al.*, (*ARS*) 475P
——, The respiratory compliance in normal and obese subjects during anaesthesia, Mulazzi, D., *et al.*, (*ESA*) A.54
Position, supine, The respiratory compliance in normal and obese subjects during anaesthesia, Mulazzi, D., *et al.*, (*ESA*) A.54
Potency, anaesthetic, Addition of droperidol to PCA morphine: what is the optimal dose? Lamond, C. T., *et al.*, (*ESA*) A.204
——, Clonal variation in response to enflurane anaesthesia with *Daphnia magna*, Myles, A. P., *et al.*, (*ARS*) 476–477P
——, Comparison of infusion rates of three i.v. anaesthetic agents for induction in elderly patients, Berthoud, M. C., *et al.* 423–427
——, Pharmacokinetics of propofol administered by infusion in dogs undergoing surgery, Nolan, A., *et al.* 546–551
——, Propofol (2,6 diisopropylphenol) as an antioxidant *in-*

vitro: a dose response study, Bennett, S., *et al.*, (*ESA*) A.152
Potency, anaesthetic, age factors, Different rates of injection of propofol, Goodman, N. W., (*C*) 383
——, Different rates of injection of propofol, Peacock, J. E., *et al.*, (*C*) 383–384
Potency, anaesthetic, ED$_{50}$, Anaesthetic properties of dimethylthiourea, Koblin, D. D., *et al.* 456–458
Potency, anaesthetic, MAC, Isoproterenol reverses the MAC decreasing effect of esmolol in rats, Perel, A., *et al.*, (*ESA*) A.117
——, Minimum alveolar concentration of sevoflurane in elderly patients, Nakajima, R., *et al.* 273–275
Potency, analgesic, Closed-loop feedback controlled administration of alfentanil during alfentanil–nitrous oxide anaesthesia, Schwilden, H., *et al.* 389–393
——, Extradural 0.07% bupivacaine for postoperative pain, Slade, J. M., (*ARS*) 478P
——, Relative efficacy and potency of nalmefene, a long-acting opioid antagonist, Watson, N. A., *et al.*, (*ARS*) 479P
Potency, drug, Anq 9040: effect of twice the ED$_{95}$ dose, Munday, I. T., *et al.*, (*ARS*) 480P
——, Onset of action of a small dose of vecuronium, Nathanson, M. H., *et al.*, (*ARS*) 481–482P
——, Potency estimation of mivacurium: comparison of two different modes of nerve stimulation, Maddineni, V. R., *et al.* 694–695
Potency, drug, age factors, Onset of action of a small dose of vecuronium, Nathanson, M. H., *et al.*, (*ARS*) 481–482P
Potency, drug, tolerance, Prolonged (> 1 week) sedation with midazolam in ICU patients: efficacy, safety and pharmacokinetics, Heytens, L., *et al.*, (*ESA*) A.178
Pregnancy, Antepartum assessment for anaesthesia, Cody, M., *et al.*, (*C*) 116
——, Antepartum assessment for anaesthesia, Reynolds, F., (*C*) 116
——, Antepartum assessment for anaesthesia, Uncles, D. R., *et al.*, (*C*) 116
——, Comparison of automatic oscillometric arterial pressure measurement with conventional auscultatory measurement in the labour ward, Hasan, M. A., *et al.* 141–144
——, Neonatal glycemia: does the maternal i.v. fluid regimen during labor make a difference? Menigaux, C., *et al.*, (*ESA*) A.175
——, Spread of spinal anaesthesia for Caesarean section in singleton and twin pregnancies, Jawan, B., *et al.* 639–641
Pregnancy, abortion, Anaesthetic implications of the anti-cardiolipin antibody syndrome, Menon, G., *et al.* 587–590
Premedication, Pharmacokinetics and effects of i.m. alfentanil as premedication for outpatient cataract surgery, Ali-Melkkilä, T., *et al.*, (*ESA*) A.145
Premedication, clonidine, Preoperative clonidine improves postoperative renal function in CABG patients, Kulka, P. J., *et al.*, (*ESA*) A.143
Premedication, glycopyrronium, Glycopyrronium prolongs topical anaesthesia of oral mucosa and enhances absorption of lignocaine, Watanabe, H., *et al.* 94–95
Premedication, guanfacine, Effects of oral preoperative guanfacine on anesthetics requirements, Engelman, E., *et al.*, (*ESA*) A.144
Premedication, lorazepam, Effects of lorazepam on oxygen saturation before cardiac surgery, Pollock, J. S. S., *et al.* 219–220
Premedication, midazolam, Dose dependent effects of oral medication with midazolam, Biro, P., *et al.*, (*ESA*) A.156
——, Midazolam premedication: a forensic approach to pharmacokinetics and amnesia, Motsch, J., *et al.*, (*ESA*) A.155
——, Plasma concentrations of midazolam after i.v., nasal or rectal administration in children, Malinovsky, J.-M., *et al.* 617–620
Premedication, nifedipine, Effect of premedication with nifedipine on intraoperative hypothermia, Vassilieff, N., *et al.*, (*ESA*) A.71
Principles and Protocols in Intensive Care, Willatts, S. M., *et al.*, (editors), (*R*) 239
Protein, albumin, Hepatic elimination of diazepam: interactions with albumin, desflurane and sevoflurane, Dale, O., *et al.* 454–455
Protein, amino acids, Glycine and its metabolites during and after intrauterine YAG laser surgery, Van Boven, M. J., *et al.*, (*ESA*) A.87
Protein, binding, Hepatic elimination of diazepam: interactions with albumin, desflurane and sevoflurane, Dale, O., *et al.* 454–455
Protein, globulin, Carbohydrate deficient transferrin: a new copredictor of alcoholism related postoperative complications? Heil, T., *et al.*, (*ESA*) A.88
Protein, metabolism, Effect of recombinant human growth hormone (HGH) on protein metabolism in surgical patients, Carli, F., *et al.*, (*ESA*) A.86
Protein, plasma, Surfactant and adult respiratory distress syndrome, Jacobson, W., *et al.* 522–526
Psychological responses, Alterations in pain threshold and psychomotor response associated with subanaesthetic concentrations of inhalation anaesthetics in humans, Tomi, K., *et al.* 684–686
——, Comparison of the sedative and amnesic effects of midazolam and propofol, Polster, M. R., *et al.* 612–616
——, Dose dependent effects of oral medication with midazolam, Biro, P., *et al.*, (*ESA*) A.156
——, Plasma catecholamines and neonatal condition after induction of anaesthesia with propofol or thiopentone at Caesarean section, Gin, T., *et al.* 311–316
——, Validation of coherent frequency of the EEG as a measure of consciousness during anaesthesia, Munglani, R., *et al.*, (*ARS*) 483–484P
Psychological responses, unconscious perception, Comparison of the sedative and amnesic effects of midazolam and propofol, Polster, M. R., *et al.* 612–616

Rabbit, Direct spinal effect of intrathecal and extradural midazolam on visceral noxious stimulation in rabbits, Crawford, M. E., *et al.* 642–646
——, Effects of hypertonic saline on coronary blood flow and myocardial performance of a blood-perfused, isolated rabbit heart, Delayance, S., *et al.*, (*ESA*) A.45
——, Functional recovery after 24 h preservation of rabbit hearts in University Wisconsin solution, Fellahi, J. L., *et al.*, (*ESA*) A.44
——, Motor blockade and absence of local nerve toxicity induced by liposomal bupivacaine injected into the axillary brachial plexus of rabbits, Legros, F. J., *et al.*, (*ESA*) A.122
——, Slow-release effect of pH-adjusted bupivacaine: pharmacokinetic demonstration, Benhamou, D., *et al.*, (*ESA*) A.120
Rat, Anaesthetic properties of dimethylthiourea, Koblin, D. D., *et al.* 456–458
——, Dexmedetomidine does not exercise its anesthetic action through GABA, Salonen, M., *et al.*, (*ESA*) A.113
——, Differential effects of specific delta and kappa opioid antagonists on the bidirectionnal effect of naloxone in arthritic rats, Cattaneo, I., *et al.*, (*ESA*) A.114
——, Effects of midazolam and flunitrazepam on the release of dopamine from rat striatum measured by *in vivo* microdialysis, Takada, K., *et al.* 181–185
——, Effects of midazolam on insulin secretion from isolated rat pancreatic islets of Langerhans, Desborough, J. P., *et al.* 221–222
——, Involvement of μ, δ, and κ receptors in the inhibition by intrathecal morphine of a C-fibre evoked reflex in the rat, Guirimand, F., *et al.*, (*ESA*) A.116
——, Isoproterenol reverses the MAC decreasing effect of esmolol in rats, Perel, A., *et al.*, (*ESA*) A.117
——, Nitrous oxide induced neuronal depression: modification through benzodiazepine receptors, Dzoljic, M., *et al.*, (*ESA*) A.112
Receptors, chemoreceptors, Effect of oral diazepam on the sensitivity of upper airway reflexes, Murphy, P. J., *et al.* 131–134
Receptors, opioid, Differential effects of specific delta and kappa opioid antagonists on the bidirectionnal effect of naloxone in arthritic rats, Cattaneo, I., *et al.*, (*ESA*) A.114
——, Effects of morphine and its metabolites on opiate receptor binding and cyclic adenosine-3′,5′-monophosphate (cAMP) formation in human neuroblastoma cells, Lambert, D. G., *et al.*, (*ARS*) 475–476P
——, Involvement of μ, δ, and κ receptors in the inhibition by intrathecal morphine of a C-fibre evoked reflex in the rat, Guirimand, F., *et al.*, (*ESA*) A.116
Records, A national database for intensive care medicine in Sweden, Karling, M., (*ESA*) A.8
Records, medical, Death certification, Baskett, P. J. F., (*C*) 112
——, Death certification, Skinner, A. C., (*C*) 112
Recovery, Flumazenil facilitates intraoperative arousal in scoliosis surgery, Koscielniak-Nielsen, Z. J., *et al.*, (*ESA*) A.157
Recovery, postoperative, Comparison of recovery from anaesthesia induced in children with either propofol or thiopentone, Runcie, C. J., *et al.* 192–195
——, Hypoxic events after general anaesthesia in the recovery room, Degasperi, D., *et al.*, (*ESA*) A.59
——, I.v. anaesthesia with propofol using a target-controlled

infusion system: comparison with inhalation anaesthesia for general surgical procedures in children, Doyle, E., *et al.* 542–555

——, Laparoscopic *vs* open cholecystectomy, Jakeways, M. S. R., *et al.*, (*C*) 597

——, Metabolic effects of propofol and flunitrazepam given for sedation after aortic surgery, Moritz, F., *et al.* 451–453

Recovery, psychomotor, Does propofol supplemented anaesthesia affect neurophysiological outcome following cardiopulmonary bypass? Phillips, A. S., *et al.*, (*ARS*) 484P

——, Evaluation of saccadic eye movements as an objective test during recovery from anesthesia, Paut, O., *et al.*, (*ESA*) A.10

——, Pharmacokinetics of flumazenil and midazolam, Jones, R. D. M., *et al.* 286–292

——, Spontaneous excitatory movements during recovery from propofol anaesthesia in an infant: EEG evaluation, Borgeat, A., *et al.* 459–461

Reflexes, baroreceptor, Cardiovascular effects of i.v. induction in children: comparison between propofol and thiopentone, Aun, C. S. T., *et al.* 647–653

——, Effects of surgical stimulation on autonomic reflex function: assessment by changes in heart rate variability, Latson, T. W., *et al.* 301–305

Reflexes, chemoreceptor, Effect of hyperoxia on the breathing of patients anaesthetized with infusions of propofol, Dow, A. C., *et al.* 532–535

——, Effects of active and passive sighs in normoxia and hyperoxia on the breathing of patients anaesthetized with infusions of propofol, Goodman, N. W., *et al.* 536–541

Reflexes, laryngeal, Effect of stopping smoking on upper airway reflexes, Erskine, R. J., *et al.*, (*ARS*) 478P

——, Measurement of the sensitivity of upper airway reflexes, Langton, J. A., *et al.* 126–130

——, Upper airway reflexes, Drummond, G. B., (*E*) 121–123

Reflexes, spinal, Differential effects of alfentanil, fentanyl, pethidine and lignocaine administered intrathecally on nociceptive responses evoked by low and high frequency stimulation of somatic nerves, Wang, C., *et al.* 63–69

——, Effect of morphine on a nociceptive flexion reflex in patients with postoperative pain, Chauvin, M., *et al.*, (*ESA*) A.115

——, Involvement of μ, δ, and κ receptors in the inhibition by intrathecal morphine of a C-fibre evoked reflex in the rat, Guirimand, F., *et al.*, (*ESA*) A.116

Risk, Explaining risk to patients, Chambers, W. A., (*C*) 381–382

——, Explaining risk to patients, Potter, F. A., (*C*) 381

——, Logistic regression analysis of fixed patient factors for postoperative sickness: a model for risk assessment, Palazzo, M., *et al.* 135–140

Safety, drug, Diamorphine/bupivacaine mixture *vs* plain bupivacaine: a comparison of epidural infusions in labour, Bailey, C. R., *et al.*, (*ESA*) A.169

——, Does etomidate cause haemolysis? Doenicke, A., *et al.*, (*C*) 491

——, Dose dependent effects of oral medication with midazolam, Biro, P., *et al.*, (*ESA*) A.156

——, High dose oral morphine in cancer pain management, Radbruch, L., *et al.*, (*ESA*) A.212

——, Motor blockade and absence of local nerve toxicity induced by liposomal bupivacaine injected into the axillary brachial plexus of rabbits, Legros, F. J., *et al.*, (*ESA*) A.122

——, Muscular paralysis and ventilatory failure caused by hyperkalaemia, Freeman, S. J., *et al.* 226–227

——, Prolonged (> 1 week) sedation with midazolam in ICU patients: efficacy, safety and pharmacokinetics, Heytens, L., *et al.*: (*ESA*) A.178

——, Veterinary use of "Xylocaine" spray, Taylor, P. M., (*C*) 113

Safety, equipment, Bacterial retention properties of heat and moisture exchange filters, Fox, D., (*C*) 382

——, Bacterial retention properties of heat and moisture exchange filters, Lee, M. G., (*C*) 382

——, Computer-controlled syringe pump improves safety of pharmacokinetic models, Duranteau, R., *et al.*, (*ESA*) A.148

——, "Concorde nose" in Whitacre spinal needles, McLeod, G. A., *et al.*, (*C*) 593

——, Frequency of damaged coaxial breathing systems, Robinson, D. L., (*C*) 384

——, Metal particle generation caused by the combined spinal–extradural technique, Hargreaves, J., (*C*) 706

——, Penetration of an aerosol, produced by film atomization, through the carinal bifurcation, Inglis, T. J. J., *et al.* 527–531

——, Possible venous air embolism with a new water jet dissector, Smith, J. A. S. 466–467

——, Spinal extradural abscess: pursuit of vigilance, Bromage, P. R. 471–473

Safety, techniques, Abdominal wall retraction may decrease anaesthesiological risks of laparoscopic cholecystectomy, Vereczkey, Z., *et al.*, (*ESA*) A.64

——, Continuous monitoring of Sp_{O_2} during total intravenous anaesthesia with ketamine and spontaneous ventilation, Joly, L.-M., *et al.*, (*ESA*) A.58

——, Continuous spirometry for detection of double-lumen endobronchial tube displacement, Bardoczky, G. I., *et al.* 499–502

——, Continuous subarachnoid infusion of 0.125% bupivacaine for analgesia during labour, McHale, S., *et al.*, (*C*) 701

——, Continuous subarachnoid infusion of 0.125% bupivacaine for analgesia during labour, Russell, R., (*C*) 699–700

——, Diaphragmatic function after bupivacaine cervical extradural analgesia for chronic pain therapy, Nyström, E., *et al.*, (*ESA*) A.65

——, Double-lumen tubes, Vaughan, R. S., (*E*) 497–498

——, EEG-monitoring during defibrillator-implantation: effects of repetitive cerebral ischemia on electric brain activity, Spies, C., *et al.*, (*ESA*) A.110

——, Effects of postoperative auto-transfusion in spine surgery, Riou, B., *et al.*, (*ESA*) A.103

——, Endobronchial cuff pressures, Cobley, M., *et al.* 576–578

——, External ventricular CSF drains infections, Mahé, V., *et al.*, (*ESA*) A.109

——, Extradural abscess in the postpartum period, Ngan Kee, W. D., (*C*) 704

——, Extradural abscess in the postpartum period, Vasdev, G. M. S., *et al.*, (*C*) 703–704

——, Face masks and spinal anaesthesia, O'Kelly, S. W., *et al.*, (*C*) 239

——, Face masks and spinal anaesthesia, Wildsmith, J. A. W., (*C*) 239

——, Fentanyl or buprenorphine side effects in spinal anaesthesia, Foppoli, R., *et al.*, (*ESA*) A.132

——, Flumazenil facilitates intraoperative arousal in scoliosis surgery, Koscielniak-Nielsen, Z. J., *et al.*, (*ESA*) A.157

——, Intrathecal pain relief in terminally ill cancer patients at home, Wagemans, M. F. M., *et al.*, (*ESA*) A.213

——, Jugular bulb metabolic monitoring during hyperventilation in severe head trauma patients, De Deyne, C., *et al.*, (*ESA*) A.106

——, Metal particle generation caused by the combined spinal–extradural technique, Hargreaves, J., (*C*) 706

——, Patient-controlled analgesia by proxy, Lam, F. Y., (*C*) 113

——, Propofol anaesthesia with spontaneous breathing for extracorporeal shock wave lithotripsy, Pasch, T., *et al.*, (*ESA*) A.153

——, Respiratory effects of laparoscopic cholecystectomy (preliminary data), Crea, M. A., *et al.*, (*ESA*) A.63

——, Safety of PCA in elderly, Santangelo, E., *et al.*, (*ESA*) A.206

——, Sedation with propofol during regional anaesthesia, Arnold, B. D. C., (*C*) 112

——, The laryngeal mask and intraocular surgery, Ripart, J., *et al.*, (*C*) 704

——, Tracheal tube cuff inflation as an aid to blind nasotracheal intubation, Van Elstraete, A. C., *et al.* 691–693

——, Use of thoracic epidural block for perioperative analgesia in children, Entress, A. H., *et al.*, (*ESA*) A.158

Scoliosis, Flumazenil facilitates intraoperative arousal in scoliosis surgery, Koscielniak-Nielsen, Z. J., *et al.*, (*ESA*) A.157

Screening, A new clinical score to predict difficult intubation, Arné, J., *et al.*, (*ESA*) A.1

——, Carbohydrate deficient transferrin: a new copredictor of alcoholism related postoperative complications? Heil, T., *et al.*, (*ESA*) A.88

——, Combined caffeine–halothane test for malignant hyperthermia, Ellis, F. R., *et al.*, (*C*) 598

——, Combined caffeine–halothane test for malignant hyperthermia, Nelson, T. E., (*C*) 597–598

——, Dipyridamole-TEE and 24 h Holter-ECG as preoperative screening tests for coronary artery disease in patients with abdominal aortic aneurysm, Östman, M., *et al.*, (*ESA*) A.22

——, Does routine preoperative coronary angiography modify outcome after aortic surgery? Gosgnach, M., *et al.*, (*ESA*) A.6

——, Indications for coronary revascularisation in vascular surgical patients, Gosgnach, M., *et al.*, (*ESA*) A.5

——, Molecular mediators and cardiac surgery, Pérez Arancón, J. L., *et al.*, (*ESA*) A.188
——, Molecular mediators and post-bacteraemic phase, Martínez Urionabarrenetxea, K., *et al.*, (*ESA*) A.187
——, Spin resonance spectroscopy to detect malignant hyperthermia susceptibility, Buckmaster, H. A., *et al.*, (*C*) 598–599
——, Spin resonance spectroscopy to detect malignant hyperthermia susceptibility, Halsall, P. J., *et al.*, (*C*) 599
Sedation, A comparison of midazolam and midazolam plus fentanyl for colonoscopy, Dupont, H., *et al.*, (*ESA*) A.9
——, Comparison of midazolam with propofol for sedation in outpatient bronchoscopy, Crawford, M., *et al.* 419–422
——, Comparison of the sedative and amnesic effects of midazolam and propofol, Polster, M. R., *et al.* 612–616
——, Dose dependent effects of oral medication with midazolam, Biro, P., *et al.*, (*ESA*) A.156
——, Metabolic effects of propofol and flunitrazepam given for sedation after aortic surgery, Moritz, F., *et al.* 451–453
——, Sedation with propofol during regional anaesthesia, Arnold, B. D. C., (*C*) 112
——, Target-controlled intravenous sedation with propofol, Mergaert, C., *et al.*, (*ESA*) A.149
Serotonin (5-hydroxytryptamine), Platelet serotonin is a mediator potentially involved in anaphylactic reaction to neuromuscular blocking drugs, Bermejo, N., *et al.* 322–325
Sheep, Influence of cardiac output, injection time and injection volume on the initial mixing of drugs with venous blood after i.v. bolus administration to sheep, Upton, R. N., *et al.* 333–338
——, I.v. bolus administration of subconvulsive doses of lignocaine to conscious sheep: myocardial pharmacokinetics, Huang, Y. F., *et al.* 326–332
——, I.v. bolus administration of subconvulsive doses of lignocaine to conscious sheep: relationships between myocardial pharmacokinetics and pharmacodynamics, Huang, Y. F., *et al.* 556–561
Skin, blood flow, Effects of intradermal lignocaine and mepivacaine on human cutaneous circulation in areas with histamine-induced neurogenic inflammation, Fruhstorfer, H., *et al.* 167–172
Sleep, A survey of sleep problems in surgical patients, Beydon, L., *et al.*, (*ESA*) A.4
Sleep apnoea, Cerebral perfusion during obstructive sleep apnea (OSA), Bålfors, E., *et al.*, (*ESA*) A.62
Solubility, lipid, Lipid solubility of pancuronium and vecuronium determined by n-octanol/water partitioning, Weindlmayr-Goettel, M., *et al.* 579–580
Solubility, partition coefficients, Asymmetry of uptake and washout of inert gases—lessons learnt in an anaesthetic department, Flook, V., (*ARS*) 487–488P
——, Lipid solubility of pancuronium and vecuronium determined by n-octanol/water partitioning, Weindlmayr-Goettel, M., *et al.* 579–580
——, Test-tube equilibration of volatile anaesthetic concentrations, Martin, D. C., *et al.* 365–367
Specialty Medical Audit (Medical Audit Series 4), Shaw, C., (*R*) 495
Spinal cord, evoked potentials, Involvement of μ, δ, and κ receptors in the inhibition by intrathecal morphine of a C-fibre evoked reflex in the rat, Guirimand, F., *et al.*, (*ESA*) A.116
Spinal cord, GABA, Dexmedetomidine does not exercise its anesthetic action through GABA, Salonen, M., *et al.*, (*ESA*) A.113
Spinal cord, motor block, Effects of intrathecal meperidine (MP), fentanyl (FN) and lidocaine (LD) on somatosensory (SSEP) and cortical motor (CMEP) evoked potentials in humans, Fernandez, S., *et al.*, (*ESA*) A.119
Spinal cord, reflexes, Direct spinal effect of intrathecal and extradural midazolam on visceral noxious stimulation in rabbits, Crawford, M. E., *et al.* 642–646
Spinal cord, sensory block, Effects of intrathecal meperidine (MP), fentanyl (FN) and lidocaine (LD) on somatosensory (SSEP) and cortical motor (CMEP) evoked potentials in humans, Fernandez, S., *et al.*, (*ESA*) A.119
Statistics, A national database for intensive care medicine in Sweden, Karling, M., (*ESA*) A.8
——, Statistical assessment of two methods of clinical measurement, Berridge, J. C., (*C*) 595
——, Statistical assessment of two methods of clinical measurement, Runcie, C. J., (*C*) 595
Sterilization, povidone-iodine, Extradural abscess in the postpartum period, Ngan Kee, W. D., (*C*) 704
——, Extradural abscess in the postpartum period, Vasdev, G. M. S., *et al.*, (*C*) 703–704
Stress, Anaesthesia affects plasma concentrations of vasopressin, von Willebrand factor and coagulation factor VIII in cardiac surgical patients, Kuitunen, A., *et al.* 173–180
——, Effect of extradural analgesia on stress responses to abdominal surgery in infants, Wolf, A. R., *et al.* 654–660
——, Influence of pneumoperitoneum and posture on hemodynamic and stress responses during anaesthesia for laparoscopic surgery, Odeberg, S., *et al.*, (*ESA*) A.34
Surgery, abdominal, Effect of extradural analgesia on stress responses to abdominal surgery in infants, Wolf, A. R., *et al.* 654–660
——, Effects of surgical stimulation on autonomic reflex function: assessment by changes in heart rate variability, Latson, T. W., *et al.* 301–305
——, Pain relief for infants undergoing abdominal surgery: comparison of infusions of i.v. morphine and extradural bupivacaine, Wolf, A. R., *et al.* 10–16
——, Postoperative hypoxaemia: comparison of epidural and patient controlled analgesia, Spencer, A., *et al.*, (*ESA*) A.207
Surgery, aneurysm, Effect of selective cell separation on respiratory function after aortic aneurysm surgery, McKavney, M., *et al.*, (*ARS*) 475P
——, Effects of oral preoperative guanfacine on anesthetics requirements, Engelman, E., *et al.*, (*ESA*) A.144
——, Extradural 0.07% bupivacaine for postoperative pain, Slade, J. M., (*ARS*) 478P
——, Influence of positive pressure ventilation on myocardial ischaemia after abdominal aortic aneurysm repair, McCoy, D., *et al.*, (*ESA*) A.43
Surgery, autonomic responses, Effects of surgical stimulation on autonomic reflex function: assessment by changes in heart rate variability, Latson, T. W., *et al.* 301–305
Surgery, bronchoscopy, Comparison of midazolam with propofol for sedation in outpatient bronchoscopy, Crawford, M., *et al.* 419–422
Surgery, cardiovascular, Accuracy of processed auditory evoked response in predicting movement during cardiac surgery, Kuppe, H., *et al.*, (*ESA*) A.31
——, Acute preoperative plasmapheresis during cardiac surgery, Armellin, G., *et al.*, (*ESA*) A.104
——, Anaesthesia affects plasma concentrations of vasopressin, von Willebrand factor and coagulation factor VIII in cardiac surgical patients, Kuitunen, A., *et al.* 173–180
——, Cardiac output determined from pulmonary gas exchange, Österlund, B., *et al.*, (*ESA*) A.19
——, Comparison of dobutamine with enoximone following open heart surgery in small children, Innes, P., *et al.*, (*ESA*) A.167
——, Does propofol supplemented anaesthesia affect neurophysiological outcome following cardiopulmonary bypass? Phillips, A. S., *et al.*, (*ARS*) 484P
——, Early postperfusion assessment of gas exchange and postoperative extubation outcome following coronary artery surgery, Knapik, P., *et al.*, (*ESA*) A.61
——, Extracorporeal membrane oxygenation for postoperative cardiac support in newborn infants: first clinical data, Marcassa, A., *et al.*, (*ESA*) A.168
——, Haemodynamic and metabolic consequences of aortic occlusion during abdominal aortic surgery, Whalley, D. G., *et al.* 96–98
——, High dose aprotinin *versus* desmo-pressin acetate treatment in cardiac surgery, Hidalgo, F., *et al.*, (*ESA*) A.99
——, Metabolic effects of corrective surgery in infants and children with congenital heart defects, Puhakka, K., *et al.* 149–153
——, Metabolic effects of propofol and flunitrazepam given for sedation after aortic surgery, Moritz, F., *et al.* 451–453
——, Molecular mediators and cardiac surgery, Pérez Arancón, J. L., *et al.*, (*ESA*) A.188
——, Pulmonary and systemic vascular effects of isoproterenol, nitroglycerin and prostaglandin E1 early after cardiac operations in patients with pulmonary hypertension, Alvarez, J., *et al.*, (*ESA*) A.27
——, The combined prophylactic administration of H1 and H2 receptor blockers in the prevention of protamine related haemodynamic effects and the relation between antihistaminics-leucocytes and pulmonary vascular resistance, Durak, P., *et al.*, (*ESA*) A.95
——, The relationship between cardiopulmonary bypass related immunologic effects and complement, thromboxane and leucocyte parameters, Durak, P., *et al.*, (*ESA*) A.96
——, Tolerance of preoperative transesophageal echocardiography in patients scheduled for aortic surgery, Gosgnach, M., *et al.*, (*ESA*) A.21
——, Use of esmolol in the postbypass management of hypertrophic obstructive cardiomyopathy, Ooi, L. G., *et al.* 104–106

——, Volume replacement with hydroxyethyl starch solution in children, Boldt, J., *et al.* 661–665

Surgery, cataract, Pharmacokinetics and effects of i.m. alfentanil as premedication for outpatient cataract surgery, Ali-Melkkilä, T., *et al.*, (*ESA*) A.145

Surgery, cleft palate, Evaluation of a forced-air warmer (Bair-Hugger) in maintaining body temperature in infants during cleft palate surgery, Murat, I., *et al.*, (*ESA*) A.166

Surgery, day-case, Neuromuscular blockers in day-case surgery: is speed of onset more important than duration of action? Lippmann, M., *et al.*, (*C*) 235

——, Neuromuscular blockers in day-case surgery: is speed of onset more important than duration of action? Mirakhur, R. K., *et al.*, (*C*) 235

——, Pharmacokinetics and effects of i.m. alfentanil as premedication for outpatient cataract surgery, Ali-Melkkilä, T., *et al.*, (*ESA*) A.145

——, Transthoracic endoscopic sympathectomy, Gilligan, S., *et al.*, (*C*) 491

——, Transthoracic endoscopic sympathectomy, Jedeiken, R., *et al.*, (*C*) 491–492

——, Transthoracic endoscopic sympathectomy, Plastow, S. E., *et al.*, (*C*) 492

Surgery, endoscopy, A comparison of midazolam and midazolam plus fentanyl for colonoscopy, Dupont, H., *et al.*, (*ESA*) A.9

Surgery, gastrointestinal, Abdominal wall retraction may decrease anaesthesiological risks of laparoscopic cholecystectomy, Vereczkey, Z., *et al.*, (*ESA*) A.64

——, Haemodynamic changes in patients undergoing laparoscopic cholecystectomy: measurement by transthoracic electrical bioimpedance, Critchley, L. A. H., *et al.* 681–683

——, Influence of pneumoperitoneum and posture on hemodynamic and stress responses during anaesthesia for laparoscopic surgery, Odeberg, S., *et al.*, (*ESA*) A.34

——, Laparoscopic *vs* open cholecystectomy, Jakeways, M. S. R., *et al.*, (*C*) 597

——, Metabolic effects of cholecystectomy, Joris, J., (*C*) 494

——, Metabolic effects of cholecystectomy, McMahon, A. J., *et al.*, (*C*) 493–494

——, Neuroendocrine changes during pneumoperitoneum for laparoscopic cholecystectomy, Joris, J., *et al.*, (*ESA*) A.33

——, Respiratory effects of laparoscopic cholecystectomy (preliminary data), Crea, M. A., *et al.*, (*ESA*) A.63

——, Transoesophageal echocardiographic assessment of haemodynamic function during laparoscopic cholecystectomy, Cunningham, A. J., *et al.* 621–625

Surgery, gynaecological, An audit of the incidence and costs associated with post operative nausea and vomiting (PONV) following major gynaecological surgery in an inpatient population, Morris, R. W., *et al.*, (*ESA*) A.2

——, Cerebral blood flow velocities (CBFV) during anaesthesia for gynaecological laparoscopic surgery, Granry, J. C., *et al.*, (*ESA*) A.32

——, Comparison of ondansetron, metoclopramide and droperidol for the prophylaxis of emetic symptoms after gynecological laparoscopic procedures, Geiger, C., *et al.*, (*ESA*) A.14

——, Efficacy of postoperative pain treatment regimens using both buprenorphine and papaveretum sequentially after abdominal hysterectomy, Green, D. W., *et al.* 626–630

——, Epidural clonidine analgesia after major gynaecological surgery, Smilov, I., *et al.*, (*ESA*) A.176

——, Glycine and its metabolites during and after intrauterine YAG laser surgery, Van Boven, M. J., *et al.*, (*ESA*) A.87

——, Long-term backache after extradural or general anaesthesia for manual removal of placenta: preliminary report, Vickers, R. J., *et al.* 214–215

——, Midazolam–alfentanil: an anaesthetic? An investigation using the isolated forearm technique, Russell, I. F. 42–46

——, Ondansetron 4 mg *vs* droperidol 1.25 mg in the prophylaxis of postoperative nausea and vomiting after alfentanil-supplemented inhalation anaesthesia, Alon, E., *et al.*, (*ESA*) A.12

——, Postoperative pain thresholds, Cook, T. M., (*C*) 110

——, Sequential spinal peridural anaesthesia for gynaecological surgery under laparoscopy, Joos, S., *et al.*, (*ESA*) A.130

——, Use of aprotinine during cytoreductive surgery of ovarian cancer, Lequeau, F., *et al.*, (*ESA*) A.97

Surgery, haemostatic response, The haemostatic response to surgery and trauma, Murphy, W. G., *et al.* 205–213

Surgery, hepatic, Possible venous air embolism with a new water jet dissector, Smith, J. A. S. 466–467

Surgery, hormonal response, Anaesthesia affects plasma concentrations of vasopressin, von Willebrand factor and coagulation factor VIII in cardiac surgical patients, Kuitunen, A., *et al.* 173–180

——, Effect of extradural analgesia on stress responses to abdominal surgery in infants, Wolf, A. R., *et al.* 654–660

——, Influence of pneumoperitoneum and posture on hemodynamic and stress responses during anaesthesia for laparoscopic surgery, Odeberg, S., *et al.*, (*ESA*) A.34

——, Neuroendocrine changes during pneumoperitoneum for laparoscopic cholecystectomy, Joris, J., *et al.*, (*ESA*) A.33

——, Volume loading and hormonal factors in the prevention of acute tubular necrosis in kidney transplantation, Mouquet, C., *et al.*, (*ESA*) A.83

Surgery, laparoscopy, Abdominal wall retraction may decrease anaesthesiological risks of laparoscopic cholecystectomy, Vereczkey, Z., *et al.*, (*ESA*) A.64

——, Haemodynamic changes in patients undergoing laparoscopic cholecystectomy: measurement by transthoracic electrical bioimpedance, Critchley, L. A. H., *et al.* 681–683

——, Influence of pneumoperitoneum and posture on hemodynamic and stress responses during anaesthesia for laparoscopic surgery, Odeberg, S., *et al.*, (*ESA*) A.34

——, Laparoscopic *vs* open cholecystectomy, Jakeways, M. S. R., *et al.*, (*C*) 597

——, Metabolic effects of cholecystectomy, Joris, J., (*C*) 494

——, Metabolic effects of cholecystectomy, McMahon, A. J., *et al.*, (*C*) 493–494

——, Neuroendocrine changes during pneumoperitoneum for laparoscopic cholecystectomy, Joris, J., *et al.*, (*ESA*) A.33

——, Preoperative skin-surface warming reduces intraoperative hypothermia, Camus, Y., *et al.*, (*ESA*) A.72

——, Respiratory effects of laparoscopic cholecystectomy (preliminary data), Crea, M. A., *et al.*, (*ESA*) A.63

——, Sequential spinal peridural anaesthesia for gynaecological surgery under laparoscopy, Joos, S., *et al.*, (*ESA*) A.130

——, Transoesophageal echocardiographic assessment of haemodynamic function during laparoscopic cholecystectomy, Cunningham, A. J., *et al.* 621–625

Surgery, laparotomy, Metabolic effects of cholecystectomy, Joris, J., (*C*) 494

——, Metabolic effects of cholecystectomy, McMahon, A. J., *et al.*, (*C*) 493–494

Surgery, laser, Glycine and its metabolites during and after intrauterine YAG laser surgery, Van Boven, M. J., *et al.*, (*ESA*) A.87

Surgery, metabolic response, Effect of extradural analgesia on stress responses to abdominal surgery in infants, Wolf, A. R., *et al.* 654–660

——, Effect of recombinant human growth hormone (HGH) on protein metabolism in surgical patients, Carli, F., *et al.*, (*ESA*) A.86

——, Metabolic effects of cholecystectomy, Joris, J., (*C*) 494

——, Metabolic effects of cholecystectomy, McMahon, A. J., *et al.*, (*C*) 493–494

——, Metabolic effects of corrective surgery in infants and children with congenital heart defects, Puhakka, K., *et al.* 149–153

Surgery, miscellaneous, A bifurcated endobronchial tube in the management of laryngotracheo-oesophageal cleft repair, Ahmad, R., *et al.* 696–698

——, A survey of sleep problems in surgical patients, Beydon, L., *et al.*, (*ESA*) A.4

——, Analgesia by wound infiltration before or after surgery in inguinal hernioraphy, Hennart, D., *et al.*, (*ESA*) A.202

——, Improvement in i.v. regional anaesthesia by re-exsanguination before surgery, Rawal, N., *et al.* 280–285

——, Pharmacokinetics of propofol administered by infusion in dogs undergoing surgery, Nolan, A., *et al.* 546–551

Surgery, neurological, Adrenaline-induced hypotension in neurosurgery, Phillips, S., *et al.* 687–688

——, Effect of esmolol *versus* lidocaine on intracranial pressure and haemodynamic responses to laryngoscopy and intubation, Samaha, T., *et al.*, (*ESA*) A.118

——, Jugular bulb metabolic monitoring during hyperventilation in severe head trauma patients, De Deyne, C., *et al.*, (*ESA*) A.106

——, Sufentanil increases intracranial pressure in patients with head trauma, Albanese, J., *et al.*, (*ESA*) A.107

——, Transcranial Doppler sonography: effect of propofol and thiopental in patients with brain tumors and brain injuries, Schregel, W., *et al.*, (*ESA*) A.105

——, Transthoracic endoscopic sympathectomy, Gilligan, S., *et al.*, (*C*) 491

——, Transthoracic endoscopic sympathectomy, Jedeiken, R., *et al.*, (*C*) 491–492

——, Transthoracic endoscopic sympathectomy, Plastow, S. E., *et al.*, (*C*) 492

Surgery, ophthalmological, Priming of atracurium with magnesium, Lampl, E., *et al.*, (*ESA*) A.139

——, The laryngeal mask and intraocular surgery, Ripart, J., *et al.*, (*C*) 704

Surgery, orthopaedic, An investigation into the effect of passive and active cutaneous warming devices on intraoperative body temperature in elderly patients, Bennet, J., *et al.*, (*ESA*) A.73

——, Anesthesia for patients ⩾ 90 years of age in emergency hip surgery, Eleftheriadis, S., *et al.*, (*ESA*) A.3

——, Blood loss during total hip replacement, Jones, N. O., *et al.*, (*C*) 235–236

——, Blood loss during total hip replacement, McSwiney, M., (*C*) 236

——, Clinical evaluation of the oesophageal heat exchanger in the prevention of perioperative hypothermia, Kulkarni, P., *et al.* 216–218

——, Double-blind comparison of ondansetron, droperidol and saline for prevention of nausea & vomiting after orthopaedic surgery, Gan, T. J., *et al.*, (*ESA*) A.13

——, Effectiveness of core warming on net transfer of body heat across the skin, Kulkarni, P., *et al.*, (*ESA*) A.70

——, Effects of recombinant-human erythropoietin on postoperative transfusion requirements in subjects undergoing major orthopaedic surgery, Faris, P. P., *et al.*, (*ESA*) A.101

——, Evaluation of the analgesic effect of metoclopramide after opioid-free analgesia, Lisander, B. 631–633

——, Fentanyl or buprenorphine side effects in spinal anaesthesia, Foppoli, R., *et al.*, (*ESA*) A.132

——, Inhibition of increase of blood thromboxane concentration by acetylsalicylic acid after release of tourniquet in lower extremity operations, Ojanen, R., *et al.*, (*ESA*) A.94

——, Intra-articular morphine for pain relief after anterior cruciate ligament repair, Joshi, G. P., *et al.* 87–88

——, Ketorolac postoperative analgesia, Al-Hasani, A., (*C*) 112–113

——, Ketorolac postoperative analgesia, Kinsella, J., (*C*) 113

——, Pain relief after anterior cruciate ligament repair, Carroll, P. H., *et al.*, (*C*) 600

——, Pain relief after anterior cruciate ligament repair, Joshi, G. P., (*C*) 600

——, Patient-controlled extradural analgesia to compare bupivacaine, fentanyl and bupivacaine with fentanyl in the treatment of postoperative pain, Cooper, D. W., *et al.* 503–507

Surgery, otolaryngological, Xylometazoline and porphyria, Platt, N. D., (*C*) 491

Surgery, paediatric, Metabolic effects of corrective surgery in infants and children with congenital heart defects, Puhakka, K., *et al.* 149–153

Surgery, phaeochromocytoma, Use of transoesophageal echocardiography to manage beta-adrenoceptor block and assess left ventricular function in a patient with phaeochromocytoma, Ryan, T., *et al.* 101–103

Surgery, spinal, Effects of postoperative auto-transfusion in spine surgery, Riou, B., *et al.*, (*ESA*) A.103

——, Evaluation of the efficacy of forced-air warmer (Bair Hugger) during spinal surgery in children, Murat, I., *et al.*, (*ESA*) A.165

——, Flumazenil facilitates intraoperative arousal in scoliosis surgery, Koscielniak-Nielsen, Z. J., *et al.*, (*ESA*) A.157

——, Preoperative autotransfusion in emergency surgery for spine trauma, Riou, B., *et al.*, (*ESA*) A.102

Surgery, thoracic, Double-lumen tubes, Vaughan, R. S., (*E*) 497–498

——, Efficacy of continuous intercostal bupivacaine for pain relief after thoracotomy, Dryden, C. M., *et al.* 508–510

——, Endobronchial cuff pressures, Cobley, M., *et al.* 576–578

——, Preoperative indomethacin for pain relief after thoracotomy: comparison with postoperative indomethacin, Murphy, D. F., *et al.* 298–300

——, Transthoracic endoscopic sympathectomy, Gilligan, S., *et al.*, (*C*) 491

——, Transthoracic endoscopic sympathectomy, Jedeiken, R., *et al.*, (*C*) 491–492

——, Transthoracic endoscopic sympathectomy, Plastow, S. E., *et al.*, (*C*) 492

Surgery, thyroidectomy, Day 0 or day 3 laryngoscopy after thyroidectomy? Lacoste, L., *et al.*, (*ESA*) A.67

——, Direct, indirect or flexible laryngoscopy after thyroidectomy? Lacoste, L., *et al.*, (*ESA*) A.66

Surgery, transplantation, Changes in blood lactate, total body oxygen delivery and consumption during liver transplantation, Carrera, J., *et al.*, (*ESA*) A.77

——, Measurement of sigmoid intramural pH during orthotopic liver transplantation, Auroy, Y., *et al.*, (*ESA*) A.76

——, Modification of the renin–aldosterone axis during orthotopic liver transplantation, de los Ríos, J., *et al.*, (*ESA*) A.75

——, Oxygen consumption is dependent upon oxygen delivery in cirrhotics undergoing liver transplantation, Piccinni, P., *et al.*, (*ESA*) A.78

——, Shunt flow and caval pressure gradient during veno–venous bypass in human orthotopic liver transplantation, Scherer, R. U., *et al.* 689–690

Surgery, urological, Propofol anaesthesia with spontaneous breathing for extracorporeal shock wave lithotripsy, Pasch, T., *et al.*, (*ESA*) A.153

Surgery, vascular, Cardiovascular effects of a pancuronium–vecuronium mixture, Doyle, M., *et al.*, (*ARS*) 486–487P

——, Determinants of systolic pressure variation in patients ventilated after vascular surgery, Beaussier, M., *et al.*, (*ESA*) A.37

——, Does routine preoperative coronary angiography modify outcome after aortic surgery? Gosgnach, M., *et al.*, (*ESA*) A.6

——, Effects of nitrous oxide (N_2O) on systemic haemodynamics, regional left ventricular (LV) function and incidence of myocardial ischaemia (MI) in vascular surgical patients with coronary artery disease (CAD), Hohner, P., *et al.*, (*ESA*) A.41

——, Effects of oral preoperative guanfacine on anesthetics requirements, Engelman, E., *et al.*, (*ESA*) A.144

——, Epidural clonidine and myocardial ischaemia after abdominal aortic surgery, Fulgencio, J. P., *et al.*, (*ESA*) A.42

——, Indications for coronary revascularisation in vascular surgical patients, Gosgnach, M., *et al.*, (*ESA*) A.5

——, The systolic pressure variation predicts response to volume loading in patients ventilated after aortic surgery, Coriat, P., *et al.*, (*ESA*) A.38

Sympathetic nervous system, Effects of surgical stimulation on autonomic reflex function: assessment by changes in heart rate variability, Latson, T. W., *et al.* 301–305

——, Prevention and treatment of hypotension during central neural block, McCrae, A. F., *et al.* 672–680

Sympathetic nervous system, adrenaline, Adrenaline-induced hypotension in neurosurgery, Phillips, S., *et al.* 687–688

——, *In vitro* effect of ephedrine, adrenaline, noradrenaline and isoprenaline on halothane-induced contractures in skeletal muscle from patients potentially susceptible to malignant hyperthermia, Urwyler, A., *et al.* 76–79

Sympathetic nervous system, adrenergic block, Adrenaline-induced hypotension in neurosurgery, Phillips, S., *et al.* 687–688

——, Use of esmolol in the postbypass management of hypertrophic obstructive cardiomyopathy, Ooi, L. G., *et al.* 104–106

——, Use of transoesophageal echocardiography to manage beta-adrenoceptor block and assess left ventricular function in a patient with phaeochromocytoma, Ryan, T., *et al.* 101–103

Sympathetic nervous system, clonidine, Effects of epidural clonidine on anaesthetic requirements and postoperative analgesia, Samsó, E., *et al.*, (*ESA*) A.205

——, Epidural clonidine analgesia after major gynaecological surgery, Smilov, I., *et al.*, (*ESA*) A.176

——, Epidural clonidine and myocardial ischaemia after abdominal aortic surgery, Fulgencio, J. P., *et al.*, (*ESA*) A.42

——, Partial reversal of the effects of extradural clonidine by oral yohimbine in postoperative patients, Liu, N., *et al.* 515–518

Sympathetic nervous system, dexmedetomidine, Dexmedetomidine does not exercise its anesthetic action through GABA, Salonen, M., *et al.*, (*ESA*) A.113

Sympathetic nervous system, dobutamine, Metabolic effects of dobutamine, Campbell, I. T., *et al.*, (*C*) 236

——, Metabolic effects of dobutamine, Oh, T. E., *et al.*, (*C*) 237–238

——, Metabolic effects of dobutamine, Smith, D. C., *et al.*, (*C*) 236–237

——, The effect of dobutamine and norepinephrine on global and splanchnic O_2 consumption, Meier-Hellmann, A., *et al.*, (*ESA*) A.185

Sympathetic nervous system, dopamine, Does exogenous dopamine reverse cardiovascular depression induced by isoflurane during thoracic epidural blockade? Raner, C., *et al.*, (*ESA*) A.49

Sympathetic nervous system, ephedrine, *In vitro* effect of ephedrine, adrenaline, noradrenaline and isoprenaline on halothane-induced contractures in skeletal muscle from patients potentially susceptible to malignant hyperthermia, Urwyler, A., *et al.* 76–79

——, Spinal anesthesia for C section: addition of phenylephrine to ephedrine for prevention of maternal hypotension, Thirion, A.-V., *et al.*, (*ESA*) A.172

Sympathetic nervous system, esmolol, Effect of esmolol *versus* lidocaine on intracranial pressure and haemodynamic responses to laryngoscopy and intubation, Samaha, T., *et al.*, (*ESA*) A.118
——, Isoproterenol reverses the MAC decreasing effect of esmolol in rats, Perel, A., *et al.*, (*ESA*) A.117
——, Use of esmolol in the postbypass management of hypertrophic obstructive cardiomyopathy, Ooi, L. G., *et al.* 104–106
——, Use of transoesophageal echocardiography to manage beta-adrenoceptor block and assess left ventricular function in a patient with phaeochromocytoma, Ryan, T., *et al.* 101–103
Sympathetic nervous system, isoprenaline, *In vitro* effect of ephedrine, adrenaline, noradrenaline and isoprenaline on halothane-induced contractures in skeletal muscle from patients potentially susceptible to malignant hyperthermia, Urwyler, A., *et al.* 76–79
——, Isoproterenol reverses the MAC decreasing effect of esmolol in rats, Perel, A., *et al.*, (*ESA*) A.117
Sympathetic nervous system, noradrenaline, Effect of fentanyl on $[^3H]$noradrenaline uptake in isolated neuronal cell preparations, Atcheson, R., *et al.*, (*ARS*) 485P
——, *In vitro* effect of ephedrine, adrenaline, noradrenaline and isoprenaline on halothane-induced contractures in skeletal muscle from patients potentially susceptible to malignant hyperthermia, Urwyler, A., *et al.* 76–79
——, Influence of norepinephrine therapy on the oxygen supply and lactate extraction rate of the liver in the septic pig, Schäfer, R., *et al.*, (*ESA*) A.184
——, The effect of dobutamine and norepinephrine on global and splanchnic O_2 consumption, Meier-Hellmann, A., *et al.*, (*ESA*) A.185
Sympathetic nervous system, pharmacology, Does captopril modify the arterial response to vasopressor substances? Le Pelley, E., *et al.*, (*ESA*) A.48
Sympathetic nervous system, phenylephrine, Spinal anesthesia for C section: addition of phenylephrine to ephedrine for prevention of maternal hypotension, Thirion, A.-V., *et al.*, (*ESA*) A.172
Sympathetic nervous system, sympathoadrenal responses, Haemodynamic and catecholamine responses to induction of anaesthesia and tracheal intubation: comparison between propofol and thiopentone, Lindgren, L., *et al.* 306–310
——, Plasma catecholamines and neonatal condition after induction of anaesthesia with propofol or thiopentone at Caesarean section, Gin, T., *et al.* 311–316
Sympathetic nervous system, xylometazoline, Xylometazoline and porphyria, Platt, N. D., (*C*) 491
Sympathetic nervous system, yohimbine, Partial reversal of the effects of extradural clonidine by oral yohimbine in postoperative patients, Liu, N., *et al.* 515–518
Systemic lupus erythematosus, Anaesthetic implications of the anti-cardiolipin antibody syndrome, Menon, G., *et al.* 587–590

Techniques in Extracorporeal Circulation, 3rd Edn, Kay, P. H., (editor), (*R*) 239–240
Temperature, body, An investigation into the effect of passive and active cutaneous warming devices on intraoperative body temperature in elderly patients, Bennet, J., *et al.*, (*ESA*) A.73
——, Core-peripheral temperature difference in early *vs* later extubation after coronary artery surgery, Knapik, P., *et al.*, (*ESA*) A.69
——, Effect of premedication with nifedipine on intraoperative hypothermia, Vassilieff, N., *et al.*, (*ESA*) A.71
——, Effect of radiant heat on the metabolic cost of postoperative shivering, Sharkey, A., *et al.* 449–450
——, Effectiveness of core warming on net transfer of body heat across the skin, Kulkarni, P., *et al.*, (*ESA*) A.70
——, Evaluation of a forced-air warmer (Bair-Hugger) in maintaining body temperature in infants during cleft palate surgery, Murat, I., *et al.*, (*ESA*) A.166
——, Evaluation of the efficacy of forced-air warmer (Bair Hugger) during spinal surgery in children, Murat, I., *et al.*, (*ESA*) A.165
——, Preoperative skin-surface warming reduces intraoperative hypothermia, Camus, Y., *et al.*, (*ESA*) A.72
Temperature, metabolism, Effect of radiant heat on the metabolic cost of postoperative shivering, Sharkey, A., *et al.* 449–450
Temperature, regulation, Clinical evaluation of the oesophageal heat exchanger in the prevention of perioperative hypothermia, Kulkarni, P., *et al.* 216–218
——, Fentanyl, as pethidine, inhibits post anaesthesia shivering, Alfonsi, P., *et al.*, (*ESA*) A.74
Temperature, skin, An investigation into the effect of passive and active cutaneous warming devices on intraoperative body temperature in elderly patients, Bennet, J., *et al.*, (*ESA*) A.73
——, Preoperative skin-surface warming reduces intraoperative hypothermia, Camus, Y., *et al.*, (*ESA*) A.72
The Complete Recovery Room Book, Hatfield, A., *et al.*, (*R*) 709
The Oxford Textbook of Clinical Pharmacology and Drug Therapy, 2nd Edn, Graham-Smith, D. G., *et al.*, (*R*) 601
Theories of anaesthetic action, cellular mechanisms, Halothane enhances forskolin stimulated cyclic adenosine-3′,5′-monophosphate formation in human neuroblastoma cells, Hirst, R. A., *et al.*, (*ARS*) 486P
——, Membrane action of volatile anaesthetics: effect of halothane on microviscosity, Appadu, B., *et al.*, (*ARS*) 477P
——, Nitrous oxide induced neuronal depression: modification through benzodiazepine receptors, Dzoljic, M., *et al.*, (*ESA*) A.112
Theories of anaesthetic action, molecular, Effects of midazolam and flunitrazepam on the release of dopamine from rat striatum measured by *in vivo* microdialysis, Takada, K., *et al.* 181–185
Theories of analgesic action, Differential effects of alfentanil, fentanyl, pethidine and lignocaine administered intrathecally on nociceptive responses evoked by low and high frequency stimulation of somatic nerves, Wang, C., *et al.* 63–69
——, Effect of fentanyl on $[^3H]$noradrenaline uptake in isolated neuronal cell preparations, Atcheson, R., *et al.*, (*ARS*) 485P
——, Effects of morphine and its metabolites on opiate receptor binding and cyclic adenosine-3′,5′-monophosphate (cAMP) formation in human neuroblastoma cells, Lambert, D. G., *et al.*, (*ARS*) 475–476P
Thromboxane, Inhibition of increase of blood thromboxane concentration by acetylsalicylic acid after release of tourniquet in lower extremity operations, Ojanen, R., *et al.*, (*ESA*) A.94
——, The relationship between cardiopulmonary bypass related immunologic effects and complement, thromboxane and leucocyte parameters, Durak, P., *et al.*, (*ESA*) A.96
Toxicity, The management of acute poisoning, Collee, G. G., *et al.* 562–573
Toxicity, hepatic, Halothane, metabolite-induced antibodies and hepatotoxicity, Kenna, J. G., *et al.*, (*ARS*) 484–485P
——, Hepatotoxicity of volatile anaesthetics, Elliott, R. H., *et al.* 339–348
Toxicity, local anaesthetics, Motor blockade and absence of local nerve toxicity induced by liposomal bupivacaine injected into the axillary brachial plexus of rabbits, Legros, F. J., *et al.*, (*ESA*) A.122
——, Plasma concentrations of bupivacaine and its enantiomers during continuous extrapleural intercostal nerve block, Berrisford, R. G., *et al.* 201–204
Toxicity, metabolites, Halothane, metabolite-induced antibodies and hepatotoxicity, Kenna, J. G., *et al.*, (*ARS*) 484–485P
Transesophageal Echocardiography, Clements, F. M., *et al.*, (editors), (*R*) 708
Transfusion, Blood loss during total hip replacement, Jones, N. O., *et al.*, (*C*) 235–236
——, Blood loss during total hip replacement, McSwiney, M., (*C*) 236
——, Effects of recombinant-human erythropoietin on postoperative transfusion requirements in subjects undergoing major orthopaedic surgery, Faris, P. P., *et al.*, (*ESA*) A.101
——, Hypertonic solutions in acute massive haemorrhage, Brimacombe, J., *et al.*, (*C*) 705
——, Hypertonic solutions in acute massive haemorrhage, Park, G. R., (*C*) 706
——, The role of recombinant growth factors in transfusion medicine, Goodnough, L. T. 80–86
Transfusion, autotransfusion, Acute preoperative plasmapheresis during cardiac surgery, Armellin, G., *et al.*, (*ESA*) A.104
——, Effects of postoperative auto-transfusion in spine surgery, Riou, B., *et al.*, (*ESA*) A.103
——, Preoperative autotransfusion in emergency surgery for spine trauma, Riou, B., *et al.*, (*ESA*) A.102

Uterus, oxytocin, Intermittent *vs* continuous extradural infusion of bupivacaine during labour, Eddleston, J. M., (*C*) 490
——, Intermittent *vs* continuous extradural infusion of bupivacaine during labour, Laishley, R. S., (*C*) 490

——, Mechanisms of ECG changes during Caesarean section (CS)—a hypothesis, Svanström, M., *et al.*, (*ESA*) A.177

Veins, cannulation, The pressor response to venous cannulation: attenuation by prior infiltration with local anaesthetic, Langham, B. T., *et al.* 519–521
Veins, complications, Possible venous air embolism with a new water jet dissector, Smith, J. A. S. 466–467
——, Quality of induction: a clinical comparison of Etomidat-Lipuro® and Hypnomidate®, Wiebalck, A., *et al.*, (*ESA*) A.154
Veins, jugular, cannulation, Use of ultrasound to evaluate internal jugular vein anatomy and to facilitate central venous cannulation in paediatric patients, Alderson, P. J., *et al.* 145–148
Veins, veno-venous bypass, Shunt flow and caval pressure gradient during veno-venous bypass in human orthotopic liver transplantation, Scherer, R. U., *et al.* 689–690
Ventilation, airway pressure, Extra inspiratory work of breathing imposed by cricothyrotomy devices, Ooi, R., *et al.* 17–21
Ventilation, analgesics, effects of, Ventilatory effects of morphine, pethidine and methadone in children, Hamunen, K. 414–418
Ventilation, apnoea, An alternative method of increasing $P\text{co}_2$ using apnoea and continuous positive airway pressure, Karlsten, R., *et al.* 411–413
Ventilation, carbon dioxide response, An alternative method of increasing $P\text{co}_2$ using apnoea and continuous positive airway pressure, Karlsten, R., *et al.* 411–413
Ventilation, continuous positive pressure, An alternative method of increasing $P\text{co}_2$ using apnoea and continuous positive airway pressure, Karlsten, R., *et al.* 411–413
Ventilation, failure, Muscular paralysis and ventilatory failure caused by hyperkalaemia, Freeman, S. J., *et al.* 226–227
Ventilation, fresh gas flow, Fresh gas requirements of an enclosed afferent reservoir breathing system in anaesthetized, spontaneously breathing adults, Barrie, J. R., *et al.* 468–470
Ventilation, hyperventilation, Jugular bulb metabolic monitoring during hyperventilation in severe head trauma patients, De Deyne, C., *et al.*, (*ESA*) A.106
Ventilation, mechanical, An alternative method of increasing $P\text{co}_2$ using apnoea and continuous positive airway pressure, Karlsten, R., *et al.* 411–413
——, Comparison of pressure support ventilation provided by two ICU ventilators, Kalfon, P., *et al.*, (*ESA*) A.182
——, Comparison of spontaneous sighs and manual inflations in anaesthetized patients breathing air and oxygen, Dow, A. C., *et al.*, (*ARS*) 474P
——, Continuous monitoring of the ventilatory mechanics during anaesthesia & intensive care, Py, C., *et al.*, (*ESA*) A.57
——, Determinants of systolic pressure variation in patients ventilated after vascular surgery, Beaussier, M., *et al.*, (*ESA*) A.37
——, Histology aspects of pulmonary barotrauma in critically ill patients with acute respiratory failure, Rouby, J. J., *et al.*, (*ESA*) A.181
——, Penetration of an aerosol, produced by film atomization, through the carinal bifurcation, Inglis, T. J. J., *et al.* 527–531
——, Propofol and alfentanil mixture, Sandin, R., (*C*) 382–383
——, Propofol and alfentanil mixture, Taylor, I. N., *et al.*, (*C*) 383
——, Recruitment of atelectasis during general anaesthesia: a CT-study, Rothen, H. U., *et al.*, (*ESA*) A.53
——, The systolic pressure variation predicts response to volume loading in patients ventilated after aortic surgery, Coriat, P., *et al.*, (*ESA*) A.38
——, Use of the laryngeal mask and face mask by inexperienced personnel, Tighe, S. Q. M., (*C*) 114–115
——, Use of the laryngeal mask and face mask by inexperienced personnel, Tolley, P., *et al.*, (*C*) 115
——, Use of the laryngeal mask and face mask by inexperienced personnel, Walker, M. B., *et al.*, (*C*) 114
Ventilation, mechanics, Continuous monitoring of the ventilatory mechanics during anaesthesia & intensive care, Py, C., *et al.*, (*ESA*) A.57
——, Continuous spirometry: an aid in the intraoperative respiratory monitoring—case reports, Bardoczky, G., *et al.*, (*ESA*) A.55
——, Influence of posture on the respiratory mechanics during anesthesia, Engelman, E., *et al.*, (*ESA*) A.56
——, The respiratory compliance in normal and obese subjects during anaesthesia, Mulazzi, D., *et al.*, (*ESA*) A.54
Ventilation, one-lung, Continuous spirometry for detection of double-lumen endobronchial tube displacement, Bardoczky, G. I., *et al.* 499–502
Ventilation, pattern, Effect of hyperoxia on the breathing of patients anaesthetized with infusions of propofol, Dow, A. C., *et al.* 532–535
——, Effects of active and passive sighs in normoxia and hyperoxia on the breathing of patients anaesthetized with infusions of propofol, Goodman, N. W., *et al.* 536–541
Ventilation, positive end-expiratory pressure, Effects of PEEP on dynamic hyperinflation in patients with airflow limitation, Tan, I. K. S., *et al.* 267–272
——, Influence of positive pressure ventilation on myocardial ischaemia after abdominal aortic aneurysm repair, McCoy, D., *et al.*, (*ESA*) A.43
Ventilation, postoperative, Early postperfusion assessment of gas exchange and postoperative extubation outcome following coronary artery surgery, Knapik, P., *et al.*, (*ESA*) A.61
Ventilation, pressure support, Comparison of pressure support ventilation provided by two ICU ventilators, Kalfon, P., *et al.*, (*ESA*) A.182
Ventilation, restricted, Effect of three different surgical prone positions on lung volumes in healthy, awake volunteers, Hennessy, N., *et al.*, (*ARS*) 475P
——, Effect on lung volumes of oxygen concentration when breathing is restricted, Baker, A. B., *et al.* 259–266
Ventilation, sighing, Comparison of spontaneous sighs and manual inflations in anaesthetized patients breathing air and oxygen, Dow, A. C., *et al.*, (*ARS*) 474P
——, Effects of active and passive sighs in normoxia and hyperoxia on the breathing of patients anaesthetized with infusions of propofol, Goodman, N. W., *et al.* 536–541
Ventilation, spontaneous, Effect of hyperoxia on the breathing of patients anaesthetized with infusions of propofol, Dow, A. C., *et al.* 532–535
——, Extra inspiratory work of breathing imposed by cricothyrotomy devices, Ooi, R., *et al.* 17–21
Ventilation, transtracheal, Extra inspiratory work of breathing imposed by cricothyrotomy devices, Ooi, R., *et al.* 17–21
Vomiting, antiemetics, Addition of droperidol to PCA morphine: what is the optimal dose? Lamond, C. T., *et al.*, (*ESA*) A.204
——, Alizapride does reduce pain on injection of propofol: comparison with lidocaine, Zaouk, G., *et al.*, (*ESA*) A.11
——, An audit of the incidence and costs associated with post operative nausea and vomiting (PONV) following major gynaecological surgery in an inpatient population, Morris, R. W., *et al.*, (*ESA*) A.2
——, Comparison of ondansetron, metoclopramide and droperidol for the prophylaxis of emetic symptoms after gynecological laparoscopic procedures, Geiger, C., *et al.*, (*ESA*) A.14
——, Double-blind comparison of ondansetron, droperidol and saline for prevention of nausea & vomiting after orthopaedic surgery, Gan, T. J., *et al.*, (*ESA*) A.13
——, Ondansetron 4 mg *vs* droperidol 1.25 mg in the prophylaxis of postoperative nausea and vomiting after alfentanil-supplemented inhalation anaesthesia, Alon, E., *et al.*, (*ESA*) A.12
Vomiting, nausea, Addition of droperidol to patient-controlled analgesia: effect on nausea and vomiting, Williams, O. A., *et al.*, (*ARS*) 479P
——, Addition of droperidol to PCA morphine: what is the optimal dose? Lamond, C. T., *et al.*, (*ESA*) A.204
——, An audit of the incidence and costs associated with post operative nausea and vomiting (PONV) following major gynaecological surgery in an inpatient population, Morris, R. W., *et al.*, (*ESA*) A.2
——, Comparison of ondansetron, metoclopramide and droperidol for the prophylaxis of emetic symptoms after gynecological laparoscopic procedures, Geiger, C., *et al.*, (*ESA*) A.14
——, Double-blind comparison of ondansetron, droperidol and saline for prevention of nausea & vomiting after orthopaedic surgery, Gan, T. J., *et al.*, (*ESA*) A.13
——, Ondansetron 4 mg *vs* droperidol 1.25 mg in the prophylaxis of postoperative nausea and vomiting after alfentanil-supplemented inhalation anaesthesia, Alon, E., *et al.*, (*ESA*) A.12
Vomiting, nausea, patient factors, Logistic regression analysis of fixed patient factors for postoperative sickness: a model for risk assessment, Palazzo, M., *et al.* 135–140

Ward's Anaesthetic Equipment, 3rd Edn, Davey, A., *et al.*, (*R*) 240
Water flea, Clonal variation in response to enflurane anaesthesia with *Daphnia magna*, Myles, A. P., *et al.*, (*ARS*) 476–477P